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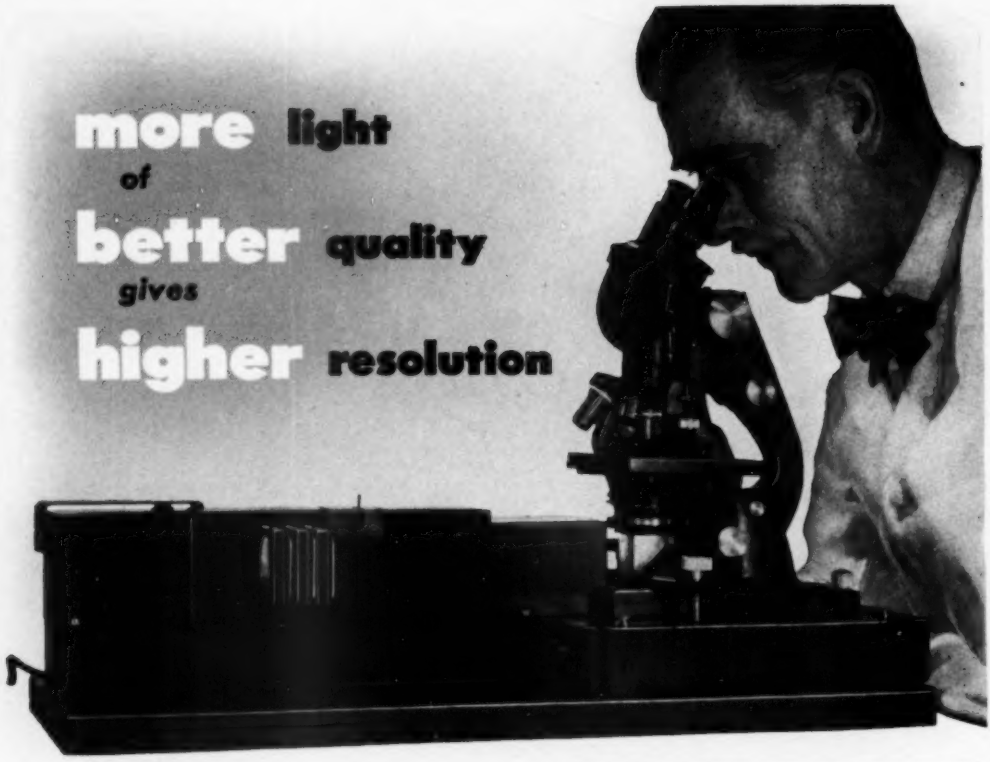

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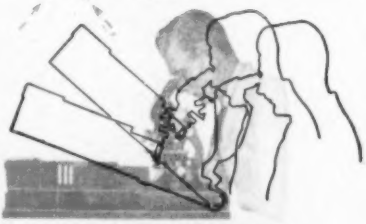

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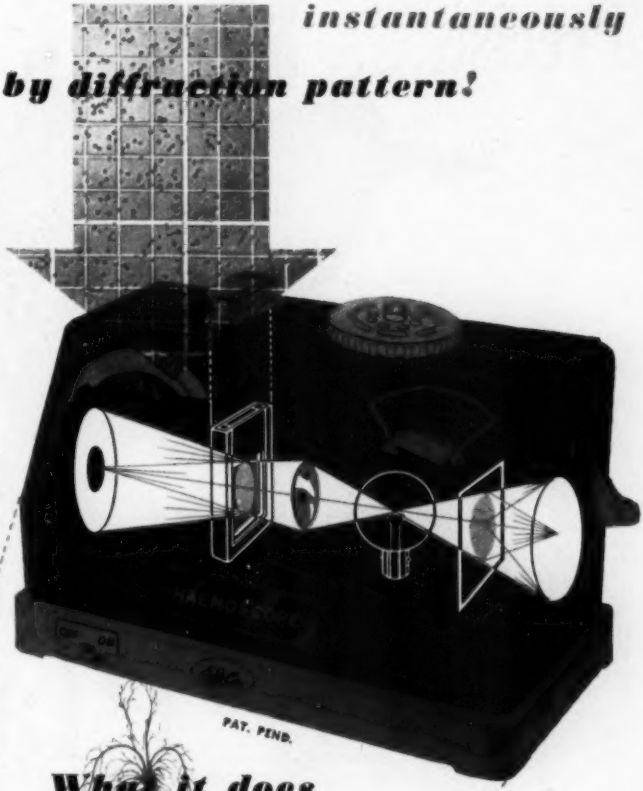

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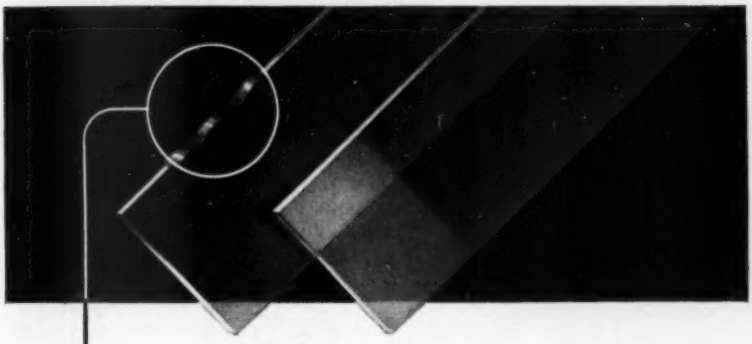

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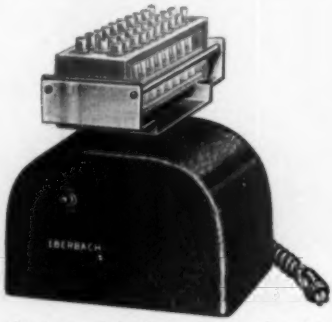

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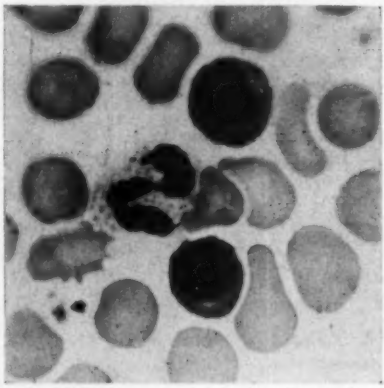

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ACCELERATED HYPERTENSIVE VASCULAR DISEASE FROM SALINE AND RENIN IN NEPHRECTOMIZED DOGS

G. M. C. MASSON, Ph.D.
GEORGE PLAHL, M.D.
A. C. CORCORAN, M.D.
AND
I. H. PAGE, M.D.
CLEVELAND

BILATERALLY nephrectomized dogs maintained alive for several weeks by vividialysis often become hypertensive and show at autopsy evidences of diffuse vascular disease.[1] This condition is associated with fluid retention, with increased inulin space, and presumably with retention and maldistribution of sodium.[2] It has recently been elicited within a few days after nephrectomy by giving a salt mixture.[3] Comparable observations have been made on bilaterally nephrectomized rats given a high-salt diet.[4]

Some years ago Winternitz and associates [5] showed that intravenous injections of renal extracts containing renin (hereafter referred to as renin) in nephrectomized dogs elicit fulminant hypertensive vascular disease resembling that which occurs in

This investigation was supported by a grant from the Heart Institute, National Institutes of Health.

From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute.

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the malignant form of experimental renal hypertension. This condition was also observed immediately after intravenous injection of renin in renal hypertensive dogs with renal excretory insufficiency elicited by partial compression of the renal arteries.[6]

Although renin is considered effective only when injected intravenously,[7] subcutaneously injected renin causes in the rat prolonged elevations of arterial pressure,[8] proteinuria, and increased urine flow.[9] Also, in rats pretreated with desoxycorticosterone acetate or with hypertonic salt solutions, it elicits an eclampsia-like syndrome characterized by hypertension, convulsions, hemorrhages, edema, renal failure, and diffuse vascular lesions.[10] Subcutaneous administration of renin has the advantage of ease; the slow absorption from a subcutaneous deposit probably simulates the hormonal release of renin substance from kidneys with altered circulation.

The present report unites and extends some of these observations. Subcutaneous injections of renin in bilaterally nephrectomized dogs are shown to precipitate "malignant hypertensive" lesions identical with those caused by intravenous injections of renin, treatment with salts, or vividialysis. The conditioning effects of salt and water and of the thyroid and adrenal glands are also examined.

METHODS AND PROCEDURES

Mongrel pound dogs of about 7 kg. body weight and in seeming good health were maintained on ground meat and fox chow while being accustomed to measurements of femoral arterial pressure by needle puncture; they were then prepared surgically for the three series of experiments.

First Series.—These experiments were designed to establish the relationship between the effects of renin and of sodium chloride loading. To this end, 38 dogs were bilaterally nephrectomized in one stage and divided into four groups. Groups I and II were untreated controls; groups III and IV received subcutaneous injections of renin. Groups I and III were given tap water to drink, while Groups II and IV were given saline (1% NaCl) instead.

Second Series.—Adrenal participation in the effect of renin on saline-fed nephrectomized dogs was examined in this series of 12 experiments. The animals were bilaterally nephrectomized and adrenalectomized in two stages at intervals of 10 days. Administration of maintenance doses (3 cc. daily in two or three equally divided doses) of lipo-adrenal cortex solution (Upjohn) was begun at the end of the second operation. The animals were then divided into two groups: Group I was treated with renin, and Group II served as control.

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Third Series.—Thyroidal influence was examined in nine dogs which were thyroidectomized and bilaterally nephrectomized 10 to 20 days later. One group of these was given renin and the other reserved as control; both were given saline to drink.

The renal extract containing renin was prepared by Dr. A. A. Green and contained 56 Goldblatt dog units per cubic centimeter. This extract was given subcutaneously three times a day, starting immediately after completion of the final surgical procedure; total doses were 3 to 6 cc. daily. Blood pressures were measured with a mercury manometer before operation and two or three times daily thereafter immediately before injection of renin. Animals were weighed at the beginning and end of the experiments.

Autopsies were performed as soon as possible after death; some moribund animals were killed for autopsy. Gross changes such as hemorrhage and edema were graded as 1 to 4+. The tissues routinely selected for microscopic examination were heart, stomach, gall bladder, colon, and urinary bladder; sections were sometimes taken from other organs, such as the eyes

Influence of Salt, Renin, Adrenalectomy, and Thyroidectomy on Blood Pressure and Morphologic Changes in Bilaterally Nephrectomized Dogs

Treatment	No. of Dogs	Blood Pressure, Mm. Hg	Gross Hemorrhages		Gross Edema		Microscopic Vascular Lesions	
			Incidence, %	Severity*	Incidence, %	Severity*	Incidence, %	Severity*
Series 1								
Water	5	123 (100-160)	80	0.6	0	0	0	0
Saline	10	135 (80-150)	100	1.2	50	1	50	0.45
Water + renin	8	158 (130-195)	100	1.5	38	0.5	75	0.9
Saline + renin	15	168 (110-205)	100	2.6	100	2	93	2.5
Series 2								
Saline + adrenalectomy	3	66 (44-80)	100	1	0	0	0	0
Saline + renin + adrenalectomy	9	154 (135-180)	100	1.1	66	1.7	33	0.5
Series 3								
Saline + thyroidectomy	3	113	100	1.3	0	0	33	0.5
Saline + renin + thyroidectomy	6	(105-125) 157 (125-185)	100	3	66	2.2	67	3.0

* Mean values based on a scale of 0 to 4+.

or brain, which presented gross lesions. The tissues were fixed in Zenker's fluid, sectioned and stained with hematoxylin-eosin-methylene blue, trichrome, periodic acid-fuchsin, phosphotungstic-acid hematoxylin, and Weigert's elastic stain.

RESULTS

Physical Manifestations

First Series.—The syndrome elicited by bilateral nephrectomy in dogs is familiar [5]; it was intensified by administration of renin. Especially noteworthy was the thirst manifested by renin-treated animals; most of these drank and vomited in alternation until they went into coma. Convulsions and bloody diarrhea developed within 24 hours, and the dogs usually died about 48 hours postoperatively; two survived for 5 days. Mean survival of controls was 4 days and 10 hours.

Data summarized in the table include values for arterial pressure. The pressures recorded are group means of the maximum pressures observed postoperatively; these were usually found 24 hours before death. Pressure was most increased in the saline-renin-treated group; seven of these showed pressures greater than 180 mm.

Hg; two, for no apparent reason, were normotensive (pressures 110 and 125 mm. Hg, respectively). Only one of the water-renin-treated group showed a pressure greater than 180 mm. Hg. Pressure was slightly greater in the saline-fed than in the water-fed controls; in the former group all but two dogs showed pressures higher than 125 mm. Hg, while in the latter only one reached this level.

Second and Third Series.—In both these series the renin-treated animals resembled those of the first series in their thirst and accelerated physical deterioration. The only noteworthy difference was the hypotension (mean, 66 mm. Hg) of the adrenalectomized saline-treated controls, as compared with the mean pressure (135 mm. Hg) in the nonadrenalectomized saline-treated animals of the first series.

Lesions

Gross.—The conspicuous lesions were hemorrhages, present in all groups, and edema, present in all but water-fed controls. The table summarizes the occurrence

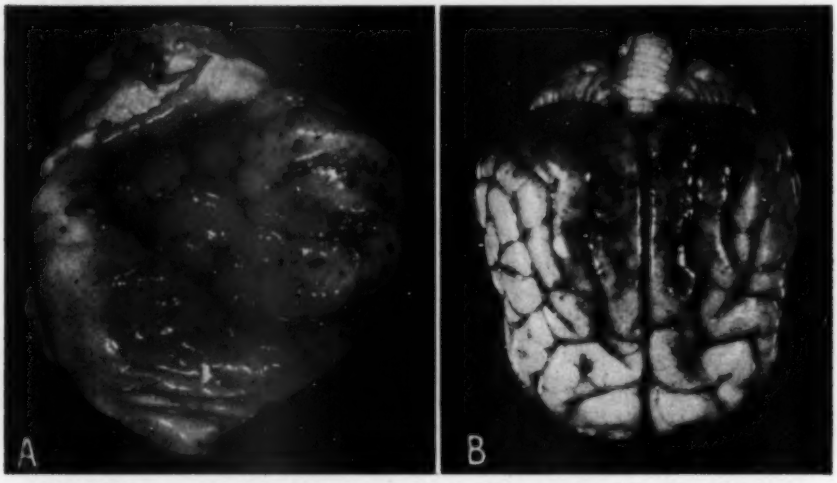

Fig. 1.—Specimens from bilaterally nephrectomized dogs given renin and saline. *A*, edema and petechiae of gastric mucosa and, *B*, confluent cerebral hemorrhages.

and relative severity of these conditions. They were most conspicuous in the saline-renin groups; they were not significantly altered by adrenalectomy or thyroidectomy. The water-fed controls showed no edema and less hemorrhage than other groups; the hemorrhages in these dogs occurred mostly in the diaphragm, colon, and heart papillary muscles.

The following description summarizes gross appearances in the saline-renin animals of the first series.

Fluid was uniformly present in the peritoneal, pleural, and pericardial sacs; the stomach, gall bladder, pancreas, and urinary bladder were severely edematous; edema of subcutaneous tissues often thickened them to a depth of 3 cm. The stomach was usually dilated and contained a large amount of saline; its mucosa was thickened and jelly-like (Fig. 1*A*). Fluid retention was also evidenced by weight gain to a maximum of 2 kg.; in contrast, the controls given only water or saline usually lost

weight. The degree of edema was not uniform, possibly because of the varying ratios between increased saline ingestion and increased vomiting. However, the tissues, including skeletal muscles, of the saline-renin animals had so uniform a wet appearance that an observer could state without prior knowledge whether or not renin had been given.

The character of the hemorrhages varied with their location (Figs. 1 and 2). Those in gastric mucosa were fundal and varied from pinpoint to 1 sq. cm. in size; hemorrhages occurred diffusely through the wall of the stomach; these extended into the esophagus, but stopped at the pylorus; they varied in their appearance with their depth in the tissue. Intestinal hemorrhages were most severe in the colon; these began as petechiae along mucosal folds, diffused, and extended through the

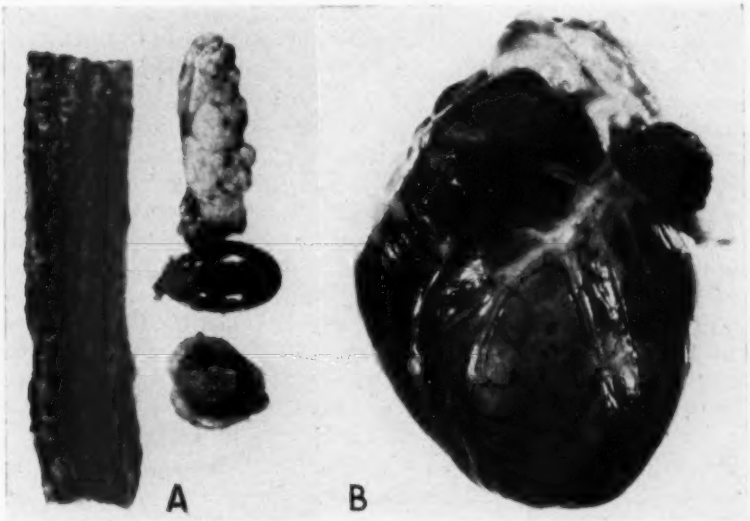

Fig. 2.—Specimens from bilaterally nephrectomized dogs given renin and saline. *A*, colon, pancreas, gall bladder, and urinary bladder, showing hemorrhages. *B*, hemorrhages and pale necrotic areas in left ventricle and hemorrhages at base of pulmonary artery.

wall of the gut; some densely hemorrhagic areas were sites of intussusception and necrosis.

The subendocardium, valves, and papillary muscles of the left ventricle were the predominant sites of hemorrhage in the heart; next affected was the base of the pulmonary artery (Fig. 2 *B*). On section, the myocardium showed alternations of yellow, necrotic areas with dark- or bright-red spots attributable to remote or recent bleeding.

The lungs were edematous and the trachea and bronchi often fluid-filled. The visceral pleura was underlain by large hemorrhagic patches.

Some of the more edematous animals showed hemorrhages in the intercostal and thoracic musculature. Discolored areas adjacent to these hemorrhages gave the impression of necrosis.

Choroidal hemorrhages were present in five animals.

The convulsions which occurred during life prompted careful examination of the brain. This organ was always found to be edematous; superficial hemorrhages were present in the cortex in some animals (Fig. 1 *B*). Serial sections commonly demonstrated areas of hemorrhage and pallor (necrosis?) in the gray matter.

Microscopic.—The major lesion demonstrable microscopically consisted of degeneration and necrosis of the smooth muscle of arterioles. Large vessels, such as the aorta, were very edematous but only slightly necrotic; very small, postarteriolar vessels were hyalinized and their lumina obstructed by necrotic accumulations. These vascular lesions were graded as to severity and incidence from 1 to 4+ without prior knowledge of the conditions of the experiment. The means of these observations are summarized in the table. In the first experimental series, vascular necrosis was most severe in the renin-saline group, less so in the water-renin group, and least severe in the group given saline without renin; vascular necrosis did not occur in the group given water and no renin. Adrenalectomy (second series) seemed to decrease somewhat the severity and incidence of vascular necrosis; thyroidectomy (third series) did not affect it.

Lesions in larger arterioles were limited to the media. The early lesions consisted of necrosis of individual muscle fibers with formation of globules of eosinophilic material; as necrosis extended, the globules coalesced and spread through the media; intima, elastica, and adventitia remained intact (Figs. 3 *B* and 4 *D*). Similar changes occurred in small arterioles, but the appearance of these differed in that media and intima were swollen and the endothelial nuclei protruded into the lumina of the vessels; also, necrosis extended irregularly into the adventitia, so that the vessels were distorted and their lumina eccentric (Fig. 3, *C* and *D*). The most severely affected vessels were diffusely necrotic, with loss of elastica and partial obliteration of their lumina; when these necrotic vessels lay in dense connective tissue, fibrillar and granular accumulations of eosinophilic material extended out beyond the vessel (Fig. 4*A*). The vascular necrosis elicited little or no leucocytic reaction.

Lesions of vessels of capillary size were hard to identify because these vessels were often included in necrotic mucosal masses. However, they could be demonstrated in the gastrointestinal submucosa and, more readily, in the brain (Fig. 5 *D*). The vessel walls were edematous and, in varying degree, hyalinized, sometimes completely; the lumina were distorted and often occluded by masses of material resembling that found in and around small arterioles. These deposits may have been carried downstream from the necrosing arterioles, and the occlusions they induced seemed to underlie necrosis and hemorrhage in such areas as the gastrointestinal mucosa. In the brain, these diseased vessels were surrounded by eosinophilic zones of nerve tissue and were associated with leucocytic invasion, hemorrhages, and encephalomalacia (Fig. 5 *C*). Similar lesions of small vessels probably accounted for the necrosis of myocardial fibers and of gastrointestinal muscle. Such thrombosed capillaries were sometimes seen as solid tubes in longitudinal sections of necrosing skeletal or cardiac muscle.

The extent of the necrotic material in and around vessels was best seen in sections stained with trichrome or periodic acid-fuchsin; with the former it was strongly fuchsinophilic and with the latter deep blue; the two stains showed the same distribution and intensity of the lesion (Fig. 3, *C* and *D*). The material was eosinophilic when stained with hematoxylin and eosin, but the lack of contrast of early lesions

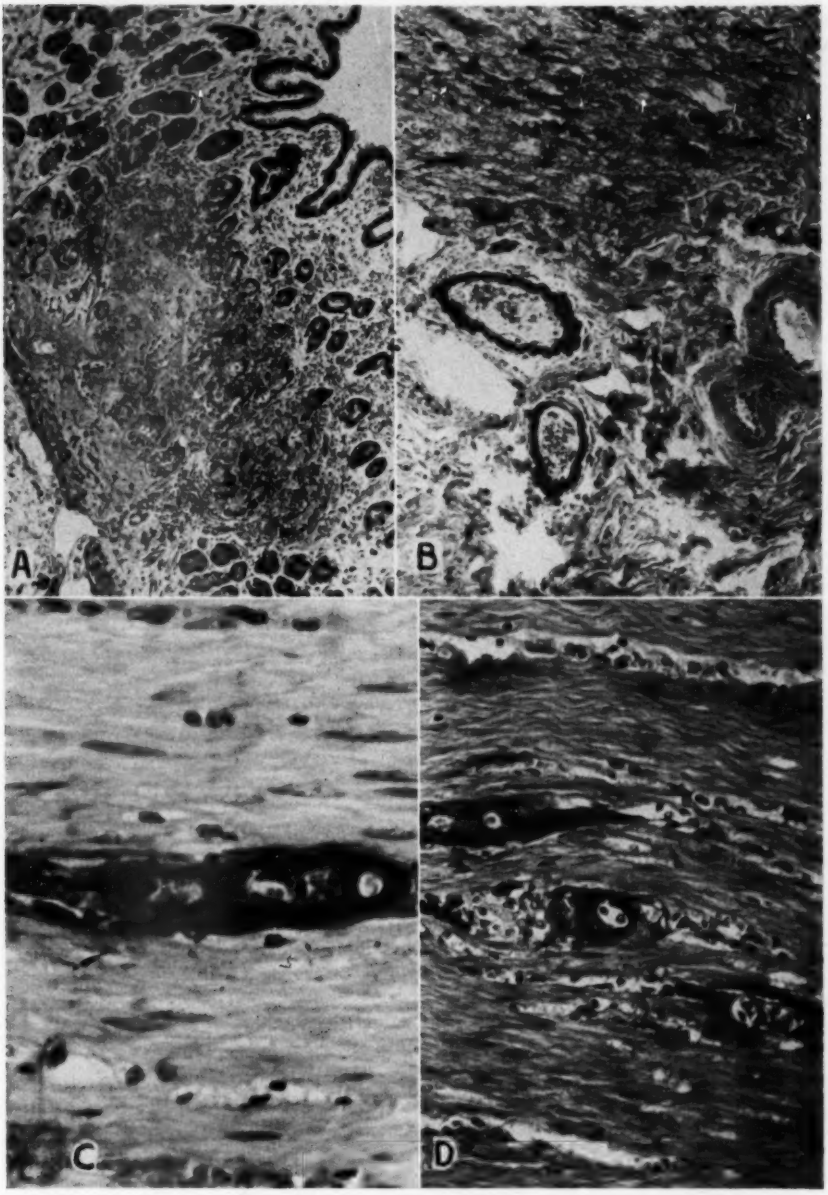

Fig. 3.—Photomicrographs of specimens from bilaterally nephrectomized dogs treated with renin and saline. *A*, gastric mucosa with hemorrhages, edema, and necrosis; hematoxylin-eosin-methylene blue, × 70. *B*, colonic submucosa, showing two small arteries with medial necrosis and one intact, together with edema of supporting tissues and presence therein of fibrillar deposits (above); trichrome, × 100. *C*, periodic acid-fuchsin stain, × 250, and *D*, trichrome stain, × 200, showing necrosis of small arterioles in muscularis of colon.

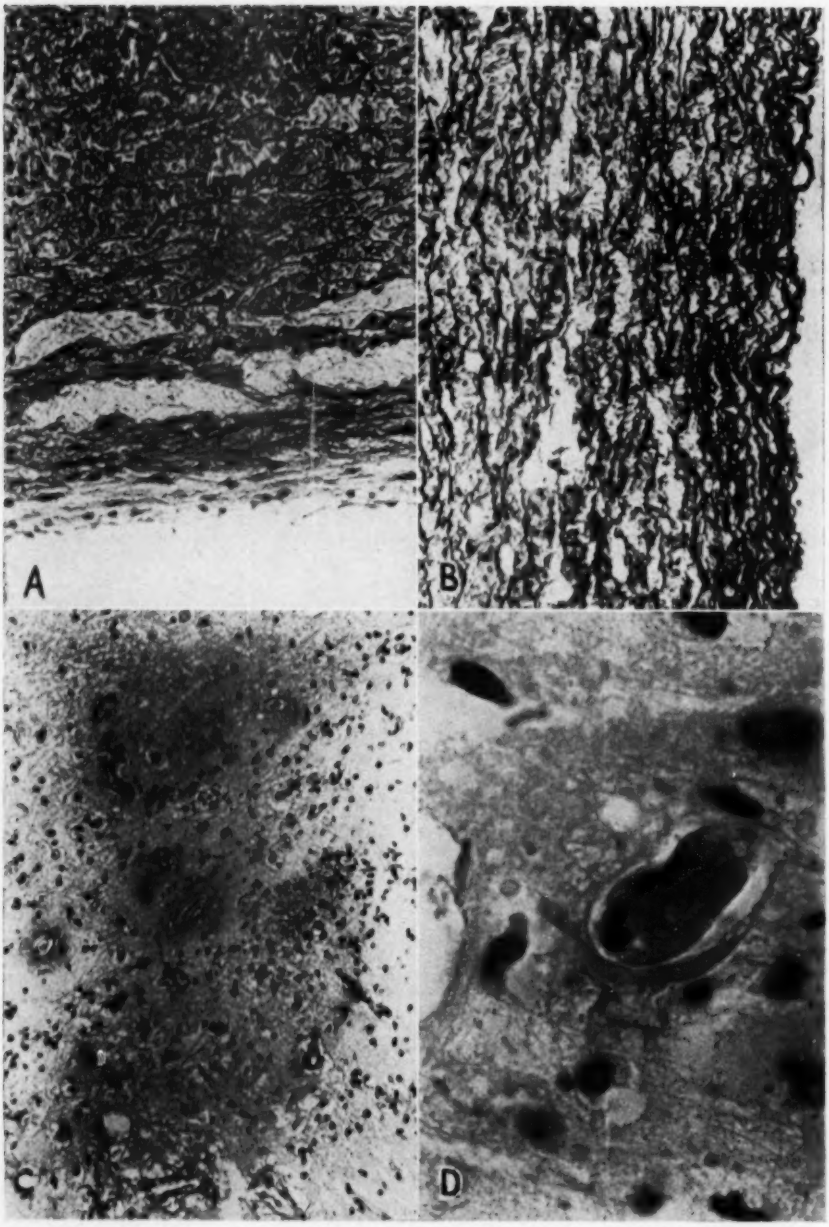

Fig. 4.—Photomicrographs of specimens from bilaterally nephrectomized dogs treated with renin and saline. Aorta (*A*, hematoxylin-eosin-methylene blue, × 200, *B*, Weigert's elastic-tissue stain with trichrome, × 200), demonstrating formation of lacunae with edema and necrosis of muscle and elastic fibers. *C*, vascular lesions with perivascular leucocytic infiltration and dispersion of eosinophilic material in brain tissue; most of the vessels are thrombosed, and (below) lacunae indicate edema and necrosis of brain tissue; hematoxylin-eosin-methylene blue, × 200. *D*, vessel of capillary size in brain, showing hyalinization of the wall, perivascular edema, and intravascular eosinophilic thrombus; hematoxylin-eosin-methylene blue; × 600.

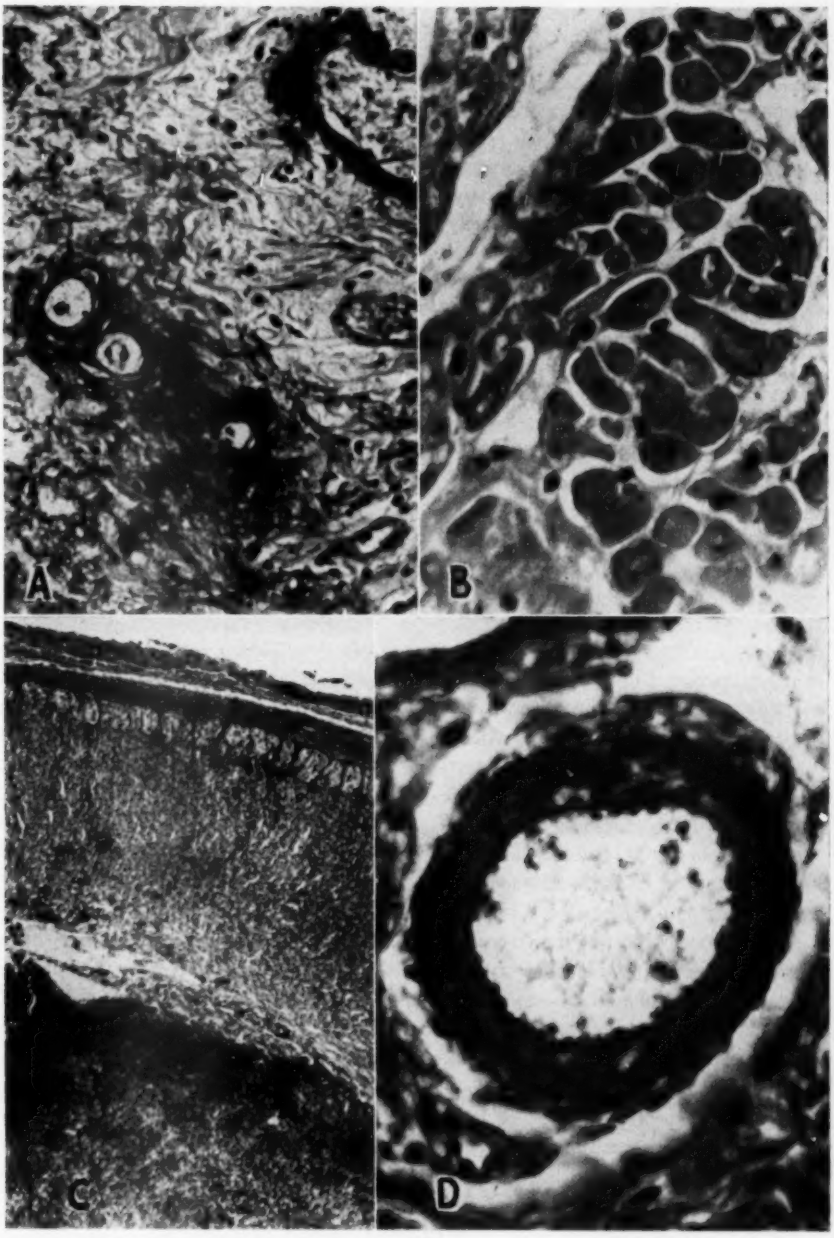

Fig. 5.—Photomicrographs of specimens from bilaterally nephrectomized dogs treated with renin and saline. *A*, colonic submucosa, showing fibrinoid necrosis, which is diffuse in small arterioles and occurs only in media of a large arteriole (upper right); trichrome, × 200. *B*, myocardium, showing vacuolization and homogenization of fibers and pyknosis of nuclei; hematoxylin-eosin-methylene blue, × 400. *C*, adrenal, showing complete medullary necrosis, petechiae in reticulata and fasciculata ,and a well-preserved glomerulosa; hematoxylin-eosin-methylene blue, × 100. *D*, arterioles, showing fibrinoid necrosis limited to the media, while the elastica remains intact; Weigert's elastic-tissue stain plus trichrome, × 600.

made them hard to identify; addition of methylene blue to this stain brought out the necrotic areas as bluish, translucent masses, which, however could not be precisely localized. Staining with phosphotungstic-acid hematoxylin varied with the vessel involved. The necrotic areas in the media of large arterioles appeared as isolated or confluent dark-blue masses; in small vessels, in which the vessel walls and surrounding tissues were diffusely involved, the larger part of the necrotic areas took an orange stain, in the center of which dark-blue masses and streaks could be seen. The blue-staining material corresponded to what is termed "fibrinoid degeneration." This differentiation in the staining properties of the necrotic areas was not evidenced with the other stains used.

Large arteries were edematous; lacunae appeared at the junction of the media and intima and occasional hemorrhages in the adventitia or adjacent media. The muscle and elastic fibers showed necrosis here and there (Fig. 5, *A* and *B*).

No vascular lesions were demonstrable in the eyes, although gross hemorrhages were found in the choroid.

The extravascular gastrointestinal and muscular lesions consisted of hemorrhage, edema, and necrosis. Edema was most severe in the stomach; there were areas of mucosal necrosis with peripheral hemorrhage and slight leucocytic invasion in which vessels could not be identified (Fig. 3*A*). The submucosa was edematous and showed the previously described lesions of necrotizing arteriolitis. Similar lesions occurred in colon, gall bladder, intestine, and urinary bladder with some differences in the proportions of edema, hemorrhage, and arteriolar necrosis; hemorrhages and necrosis predominated in the colon and edema and hemorrhages in the gall and urinary bladders.

Muscular lesions were regularly found in the myocardium, intestine, and diaphragm and often in the thoracic skeletal musculature. Muscle necrosis was usually most severe in the heart, where it was associated with extensive hemorrhagic and vascular lesions. Myocardial fibers lost their striations and became swollen and vacuolated; their nuclei became pyknotic and the fibers took up methylene blue or light green; some fibers were reduced to masses of necrotic material (Fig. 4*B*). Muscle lesions were not as extensive or severe in the gastrointestinal tract, even when the vessels were severely necrotic; necrosis here involved individual fibers or groups of fibers which became swollen, with the cytoplasm irregular in density. The skeletal-muscle lesions resembled those of the myocardium.

The adrenals often showed complete medullary necrosis. This sometimes extended into the zona reticularis, and hemorrhages were present in the zona fasciculata. Probably because of its special blood supply,[11] the zona glomerulosa was intact, although capsular arterioles were often necrotic (Fig. 4*C*). The adrenal lesions did not occur in Control Group IV, so they cannot be considered remote effects of nephrectomy as such.

COMMENT

Lesions of malignant hypertension have previously been elicited by intravenous injections of renin in dogs with total [5] and subtotal [6] renal insufficiency. Our data show that renin is at least as active in this regard when it is injected subcutaneously.

11. Harrison, R. G.: A Comparative Study of the Vascularization of the Adrenal Gland in the Rabbit, Rat and Cat, J. Anat. **85**:12, 1951.

Indeed, in one dog to which we gave 5 cc. of renin intravenously daily for three days in the manner of Winternitz and associates,[5a] arterial pressure was only moderately increased and no vascular lesions were found at autopsy. Subcutaneously injected renin did not elicit the thromboses of large vessels found in animals given intravenous injections of renin and other tissue extracts.[5b] The lesions are therefore not due to nonspecific thrombogenic properties of the kidney extract.

In this connection, Duguid's attribution [12] of arteriolar hyalinization and necrosis to deposition, organization, and inclusion of thrombi in the vessel wall will not account for the lesions we observed. Those of larger arterioles were limited to the media, while intima and elastica remained intact; further, organization of an intravascular thrombus would not be complete during the brief course of our experiments. The effectiveness of subcutaneous as well as intravenous injection of renin in precipitating lesions makes it unlikely that the lesions arise from some anaphylactic response [6b] peculiar to the nephrectomized dog.

Rather, the vascular lesions are identical with those found in nephrectomized dogs maintained by vividialysis [13] or given salt mixtures [3] and with those of malignant experimental renal hypertension.[14] The rate of their development varies with the experimental condition; it is variable in hypertension, slow in vividialysis, faster during treatment with salt mixtures, and fulminant in dogs given renin and saline.

There is abundant evidence that renal insufficiency predisposes to malignant hypertension.[7] This predisposition is believed to stem, on the one hand,[15] from deficiency of a protective renal incretory product and, on the other,[16] from an undefined characteristic of the uremic state. Our data support neither view. Control animals given neither renin nor salt did not become hypertensive during their survival. Rather, the determining factor seems to be the inability of the animal to rid itself of salt and fluid loads. Thus, in vividialysis, the factor which conditions the onset of hypertension and the development of lesions seems to be provision of excess sodium and fluid; such was also the case in Orbison's experiments; in both situations the participation with this factor of a hypothetical extrarenal "renin" has not been excluded.[17]

The mechanism by which salt and fluid loads participate in eliciting malignant hypertension is obscure. As concerns renin itself, nephrectomy is known to enhance its pressor activity; in our experiments, subcutaneously injected renin did not cause tachyphylaxis. The prolonged, intense increase of arterial pressure thus obtained may account in part for the acceleration of vascular lesions conditioned by sodium

12. Duguid, J. B.: The Arterial Lining, Lancet **2**:207, 1952.

13. Kolff, W. J., and Fisher, E. R.: Pathologic Changes After Bilateral Nephrectomy in Dogs and Rats, Lab. Invest. **1**:351, 1952. Muirhead and associates.[1]

14. Winternitz, M. C., and Waters, L. L.: Lesions of the Larger Vessels Following Renal Artery Constriction, Yale J. Biol. & Med. **12**:451, 1940. Durlacher, S. H., and Winternitz, M. C.: Studies on the Relation of the Kidney to Cardiovascular Disease: Lesions of the Myocardium, ibid. **14**:269, 1942. Goldblatt.[7]

15. Grollman, A.: Experimental Studies on Hypertension, in Hypertension: A Symposium, Minneapolis, University of Minnesota Press, 1951.

16. Pannier, R.: Le myocarde dans l'ischémie rénale expérimentale, Rev. belge path. et méd. expér. **21**:420, 1952. Goldblatt.[7]

17. Dumont, L.: Contribution à l'étude de l'hypertension artérielle par ischémie rénale, Thesis, Liége, University of Liége, 1946.

and fluid. The partial protection observed in adrenalectomized dogs can on this basis be viewed as resulting from their relatively low arterial pressures.

But there seem to be other than mechanical factors which involve a final common pathway of vasopressor and vasotoxic activities of salt and renin. Evidence summarized elsewhere [18] led to the concept that renin, apart from its pressor action, elicits a change in electrolyte balance and that this displacement is countered by increased adrenal-cortex "mineralocorticoid" function. This effect of renin is considered to reflect an aspect of its renal action, since it is associated in intact dogs or rabbits with sodium and water diuresis.[19] However, we were impressed by the thirst elicited by renin in nephrectomized dogs; this thirst can best be attributed to an extrarenal action of renin on the distribution and concentration of electrolytes. Other examples of the interaction of sodium and renin are the enhanced pressor activity of renin in sodium-treated rats [8] and the eclampsia-like syndrome which appears in rats treated with salt desoxycorticosterone after subcutaneous injection of renin.[10] The participation in the genesis of the lesions of factors which modify tissue electrolytes and permeability is also suggested as a partial explanation of the effect of adrenalectomy in these experiments and the experiments of others.[20] Negatively, the ineffectiveness of surgical thyroidectomy in modifying the course of the lesions caused by nephrectomy plus saline plus renin indicates that the determinant is some factor other than vascular (pressor) responsiveness as such, since this function is damped by suppression of thyroid function.[21]

The possibility that renin may act deleteriously in some other way than by increasing arterial pressure is also suggested by the nature of the lesions. These were of two major types. One was necrosis of vascular and extravascular muscle cells; the other was necrosis of the walls of small vessels, associated with what seemed to be extrusion of a protein through the wall and formation of a perivascular deposit. The latter lesion seems to imply increased permeability of the vessel wall. This is presumably an effect of renin, since renin is known to increase permeability of glomerular capillaries [22] and may act similarly in other, less readily observed vascular beds. Altered permeability may also underlie the lesions of muscle fibers, both

18. Corcoran, A. C.; Page, I. H.; Masson, G. M. C.; Taylor, R. D., and Dustan, H.: Hypertension and Hypertensive Cardiovascular Disease, A. M. A. Arch. Int. Med. **87**:732, 1951. Muirhead and associates.[1]

19. Merrill, A.; Williams, R. H., and Harrison, T. R.: The Effects of a Pressor Substance Obtained from the Kidneys on the Renal Circulation of Rats and Dogs, Am. J. M. Sc. **196**:240, 1938. Hughes-Jones, N. T.; Pickering, G. W.; Sanderson, P. H.; Scarborough, H., and Vandenbrucke, J.: The Nature of the Action of Renin and Hypertension on Renal Function in the Rabbit, J. Physiol. **109**:288, 1949.

20. Toussaint, C.: Les modifications pathologiques provoquées par l'ischémie partielle du rein, l'hydronéphrose bilatérale et la néphrectomie totale chez le rat intact et chez le rat surrénalectomisé, Rev. belge path. et méd. expér. **21**:464, 1952. Tripod, J., and Meier, R.: La désoxycorticostérone—percortene—Facteur de perméabilité vasculaire périphérique, Arch. Internat. pharmacodyn. **89**:311, 1952.

21. Page, I. H., and McCubbin, J. W.: Influence of Thyroidal Function on Vascular Reactivity in Dogs, Circulation **5**:390, 1952.

22. Addis, T.; Barrett, E.; Boyd, R. I., and Ureen, H. J.: Renin Proteinuria in the Rat: I. The Relation Between the Proteinuria and the Pressor Effect of Renin, J. Exper. Med. **89**:131, 1949.

vascular and extravascular; these fibers seem successively to become hydropic, disrupted, and necrosed. Such changes in permeability presumably reflect or are associated with the effect of renin on electrolyte distribution.

In brief, the data at hand suggest that the nonpressor aspects of renin action, as well as its pressor action together with other factors, such as sodium repletion, may be important determinants in the genesis of hypertensive vascular disease.

SUMMARY AND CONCLUSIONS

Subcutaneous injection of renin in nephrectomized dogs maintained on 1% NaCl as drinking fluid elicits a syndrome of accelerated malignant hypertension characterized during life by thirst, edema, and hemorrhage and at autopsy by lesions of vascular and extravascular muscle fibers. These conditions are identical with those observed in dogs with malignant experimental renal hypertension and in nephrectomized dogs sustained by vividialysis or given salt mixtures. Renin acts similarly but less intensely in nephrectomized dogs maintained on water. Adrenalectomy ameliorates the disease in nephrectomized dogs given renin plus saline, while thyroidectomy has no effect on the process.

The prolonged, sustained increase of arterial pressure caused by subcutaneously injected renin in nephrectomized dogs accounts in part for the acceleration of vascular lesions. However, their nature, their association with necrosis of extravascular muscle, and the many evidences which associate renin with the sodium ion in problems of vascular disease indicate that renin may also act by changing the distribution of electrolytes in and around cells, thus altering their permeability to proteins and ultimately causing their death.

ENDOTHELIOMA OF CORPORA CAVERNOSA OF PENIS

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ENDOTHELIOMA of the corpora cavernosa of the penis is a rare tumor having certain unique and interesting features. Only fourteen cases have been reported in the medical literature, and in some of these the details are meager and difficult to obtain. The occurrence of two examples of this unusual tumor in the Urological Service of the Royal Victoria Hospital within a comparatively short time has prompted me to review the subject, analyze the cases which have already appeared, and report the clinical and pathological findings in these two cases.

While there is some difference of opinion as to whether certain of the tumors previously described and designated as endotheliomata actually belong in this category, it is generally accepted that tumors of this group take their origin from the lining cells of the corpora cavernosa.

Since the work of Henle [1] it has been realized that the body has three types of cavernous tissue. These are the erectile, the compressible, and a third type, which occupies a rather intermediate position between the other two. Erectile tissue is found only in the corpora cavernosa of the penis and of the clitoris, and its spaces are usually collapsed and relatively free of blood. The compressible type, however, is present about many of the openings of the body. It lies beneath the mucous membrane, and its wide venous spaces are filled with blood except when compressed by dilatation of the lumen at the orifice. In the penis it is found about the mucous membrane of the urethra, where it consists of a network of wide blood spaces lined by endothelium and having no muscle cells in the walls. The intermediate type of cavernous tissue occurs in the corpus cavernosum urethrae, also referred to as the corpus spongiosum, and in the glans.

The corpora cavernosa penis are paired structures which tend to fuse in the middle portion, or body, while proximally their crura diverge and taper off into a fibrous attachment to the periosteum on each side of the pubic arch. Distally they come to a point in the glans. Transverse section through the middle portion reveals that the corpora are united into a kidney-shaped structure with an indentation above, through which course the dorsal vessels, and a concave surface below, which is occupied by the urethra and its corpus spongiosum.

From the Department of Pathology, Division of Surgical Pathology, McGill University.

Presented at the Annual Meeting of the Quebec Association of Pathologists, Montreal, May 2, 1952.

Permission to report the cases was granted by Dr. Emerson C. Smith and Dr. Allan B. Hawthorne, of the Department of Urology, Royal Victoria Hospital.

Dr. Odoska Morganti made translations of the original papers from the Italian and Dr. Satoru Watanabe made translations of papers from the Japanese medical literature.

1. Henle, J.: Männlicher Geschlechtsapparat, in Handbuch der systematischen Anatomie des Menschen, Ed. 2, Braunschweig, F. Vieweg & Son, 1873, Vol. 2, pp. 362-445.

Histologically the cavernous bodies are found to be surrounded by a dense fibrous elastic membrane with a peripheral longitudinal and inner circular layer. In the posterior part, this tunica albuginea forms a fibrous partition between them, and here on the inner surface there is a layer of dense connective tissue containing many small veins, which drain the cavernous spaces.

The erectile tissue is a sponge-like structure consisting of trabeculae and irregularly shaped spaces, which are relatively free from blood when the organ is in a flaccid state. These spaces are lined by endothelium which is continuous with that of the arteries and veins. The trabeculae consist for the most part of smooth muscle cells which course in all directions without apparent arrangement. Between them are fine elastic fibers with occasional connective-tissue fibers and histiocytes. In the central portion of each corpus the blood spaces tend to be large, with thin muscular trabeculae free of blood channels, but toward the periphery the spaces are smaller and the trabeculae thicker, with less muscle, more elastic tissue, and occasional capillaries and veins.

A review of the 14 cases of endothelioma of the penis which have been reported would make it appear that there are both benign and malignant forms, though this distinction has not been emphasized. As the examples are comparatively few, the salient features of each will be briefly summarized so far as the information is available.

In 1883 Maurer[2] in an inaugural dissertation at the University of Halle described what is apparently the first case of this tumor to be reported. It concerned a 50-year-old man who attended Volkmann's Clinic. Lumps in both inguinal regions had been present for about three months and had been incised. There was no complaint about the penis, but on examination it was found to be swollen in a half-erect condition and to be extremely firm and hard. The patient died within a month, and autopsy revealed an abscess in the right iliac fossa which had developed as a complication of the incision of the inguinal tumor and extended to the neck of the femur. Numerous small nodules were present in and under the skin throughout the body, but the internal organs were free. The corpora cavernosa of the penis and urethra were uniformly hard and infiltrated by a yellowish-white growth, from which on section a milky fluid exuded. Microscopically the tunica albuginea appeared completely normal, and the musculoelastic walls separating the cavernous spaces were merely infiltrated by small round cells, without appreciable thickening. The spaces, however, were lined by a mantle or completely filled by a mass of round, spindle, or occasionally cylindrical tumor cells, which tended to form syncytial masses in some areas while in others cytoplasmic boundaries were well defined. These cells stained intensely with carmine, and wherever they were present the normal endothelium was missing and had not proliferated as a covering over the growth. Red blood cells were found in the lumina not completely filled by tumor, and there was considerable necrosis. Histologically the malignant cells in the metastases showed the same appearance. Maurer designated the tumor an endothelioma intravasculare.

2. Maurer, M.: Über einen eigentümlichen Fall von Angiosarkom: Endothelioma intravasculare penis, Inaugural Dissertation, Halle, 1887.

Alexander and Dunham [3] in 1897 reported from Bellevue Hospital in New York City the case of a man about 50 years of age who had noticed six months before that his penis curved upward during erection and that there was a small lump at the point of greatest curvature. This lump had increased in size. An indurated mass which was painless and measured 2.5 cm. long by 2.75 cm. broad was situated 1 in. from the symphysis pubis. The skin over it was normal in appearance and freely movable. The mass was elastic, was firmly attached to the fibrous sheath, and extended from the middle line equally into each corpus cavernosum. It did not involve the corpus spongiosum, and there was no obstruction to urination. The inguinal nodes were free. When the mass was excised the tunica was much thickened and the tumor was found to involve about a third of each corpus and was not encapsulated. Hemorrhage was controlled by pressure, and the wound healed by primary union. No recurrence of the growth on the penis had appeared when the patient was last seen, 27 months postoperatively; however, the patient died within three years without the cause of death being ascertained. Histologically the tumor presented an alveolar structure, the alveoli having a plexiform arrangement and evidently communicating with each other. They seemed to lie in the sinuses and were separated by fibromuscular trabeculae. Some invasion of the walls of the trabeculae appeared to have taken place, and there was some new fibrous stroma. The neoplastic cells varied greatly in size and shape and contained large oval vesicular nuclei with prominent nucleoli. The cytoplasm was granular, and near the middle of the larger groups degenerative fusion into highly refracting, apparently homogenous, material had occurred. These groups in occasional areas somewhat resembled the pearl formation of epitheliomata. There was some round cell infiltration, but no red blood cells were observed within the alveoli. Mitotic figures were present. The authors considered the growth as being malignant and taking origin from the endothelial lining of the sinuses. Colmers,[4] several years later, disagreed with this conclusion on the grounds that newly formed fibrous tissue was present, no free or destroyed erythrocytes were found within the tumor, invasion of trabeculae had occurred, and the endothelium of the sinuses was occasionally intact between the alveoli and the trabecular wall. It appeared to him much more likely that the tumor had taken origin from the endothelium of lymph spaces.

During the same year Tripke [5] reported in an inaugural dissertation at Würzburg, Germany, a rare case of sarcomatous degeneration of a corpus cavernosum of the penis which may well have belonged to the endotheliomata. We were unfortunately unable to obtain any detailed information concerning it.

A tumor of the penis which led to considerable controversy at the time was reported by Professor Hildebrand [6] in 1898 under the title of endothelioma intravasculare. It occurred in a man of 68 whose only complaint was a persistent

3. Alexander, S., and Dunham, E. K.: Endothelioma of the Corpora Cavernosa: Report of a Case, J. Cutan. & Genito-Urin. Dis. **15**:247, 1897.

4. Colmers, F.: Über Sarkome und Endotheliome des Penis: Im Anschluss an die Beobachtung eines Blutgefässendothelioms der Corpora cavernosa, Beitr. path. Anat. **34**:295, 1903.

5. Tripke, A.: Ein seltener Fall von sarcomatöser Degeneration des Corpus cavernosum Penis, Inaugural Dissertation, Würzberg, 1897.

6. Hildebrand: Über Resection des Penis wegen eines Endothelioma intravasculare, Deutsche Ztschr. Chir. **48**:209, 1898.

dribbling after micturition. It was as large as a dove's egg and situated slightly to the left on the under side of the organ halfway between the corona of the glans and the scrotal attachment. It was as hard as cartilage and unattached to the overlying skin. A medium-sized sound could be passed easily up the urethra to the right of it; however, the passage was followed by a trace of blood. There was no enlargement of lymph nodes. The patient, who appeared otherwise healthy, stated that he had noticed the mass first about a year before, when it was the size of a cherry stone. Although at operation the tumor appeared to be situated in the corpora cavernosa, it lay so close to the urethra that extirpation required removal of 3.5 cm. of the urinary tube, together with the tumor mass and some surrounding cavernous tissue. The remaining portions of the organ were brought together, and the patient made an excellent recovery without bleeding or fistula formation. No recurrence had taken place six months later. Hildebrand gave a very detailed gross and microscopic description of the specimen, but unfortunately there are no illustrations. The salient features were as follows. The tumor was confined to the corpus cavernosum urethrae with only flattening of the erectile tissue of the penis. The mucous membrane of the urethra was intact except for an area 4 mm. square, where it appeared eroded and was replaced by small warty excrescences. The growth consisted of branching aggregates of closely packed, small, short-spindle or polygonal cells with small round or oval nuclei. Cytoplasmic boundaries were poorly defined, but there was no pearl formation. The cords of tumor cells appeared to fill partly or completely the cavernous spaces, with loss of their endothelial lining. Growth sometimes broke across the fibromuscular septa or invaded neighboring spaces. There was some tendency for the cells to become cylindrical at the outer edge of the cords and about the vessels. A certain amount of necrosis, fibrous stroma, and round cell infiltration was present. At the area of defect in the mucous membrane of the urethra, the growth formed a wedge, the narrow point of which reached the surface as warty excrescences. The mucous glands were swollen, hyperplastic, and surrounded by small round cells. The author after a very thorough analysis of all the evidence came to the conclusion that the tumor was an endothelioma intravasculare. Borrmann [7] in a later critical review considered it a carcinoma arising from the urethra, and Colmers,[4] on the ground that free blood corpuscles were found not in the tumor tissue but only in small vessels, was inclined to accept Borrmann's diagnosis or the possibility that the tumor had arisen from the endothelial lining of the lymph spaces.

Colmers' [4] own case, together with an extensive review of the subject and the literature up to that time, was published in 1903. It concerned a man of 56 who came to the clinic because of painful erection. The pain was first experienced two months before and had become constant, was worse at night, and extended into the inguinal region. Physical examination was negative except with regard to the genitalia. On the back and under the skin of the enlarged and firm penis, which showed phimosis, were several bean-sized firm nodules as well as solid lymph tracts. The swelling and firmness extended back into the perineum, but the inguinal glands were not noticeably enlarged or tender. The urine was passed easily and was free from blood and pus. Because of the possibility that a carcinoma might be

7. Borrmann: Zum Wachstum und zur Nomenklatur der Blugefässgeschwülste, Arch. path. Anat. **157**:297, 1899.

present, the phimosis was first relieved. No break in the surface of the glans was found, but several flat nodules could be felt beneath. Three weeks later, during which the pain in the penis became constant and so severe it could not be relieved by morphine, a large lymph node at the side and close to the scrotum was removed for biopsy. Four days later amputation of the pars pendula was carried out. At the operation, as soon as the skin had been incised the distal portion broke off in the hands of the surgeon and a thick chocolate-colored purulent-appearing fluid exuded from the proximal stump. There was little actual bleeding. The patient died a week after operation with extreme dyspnea. Autopsy revealed extension backward of the growth to involve the bladder, prostate, seminal vesicles, inguinal glands, and abductor muscles of the thigh. The testes and spermatic cords were free. Metastasis had occurred to the lungs, with spread to the pericardium and right myocardium. Examination of the surgical specimen showed the mucous membrane to be intact; however, both the corpora cavernosa of the penis and that of the urethra were so infiltrated that it was impossible to determine which was the primary source. Histological examination revealed the tumor cells to be round, oval, or polygonal and rather epithelial in appearance, with pale, poorly staining cytoplasm and vesicular, often mitotic nuclei. The cells tended to fuse into multinucleated masses. They filled the sinuses, with loss of the endothelial lining, had no stroma or intercellular substance, and were not supplied by newly formed vessels. The preexisting veins were filled with blood and often thrombosed, but the arteries appeared collapsed and empty. There were considerable central necrosis and some infiltration by small round cells. Colmers made a diagnosis of endothelioma which arose from the endothelium of the sinuses of the corpora cavernosa and was comparable to the tumor previously described by Maurer.

A remarkable case in which the question of a diagnosis of endothelioma of the corpora cavernosa arose was reported by Creite [8] from Göttingen, Germany, in 1905. It concerned a 2-year-old child who was brought to the clinic because of a marked priapism which had developed slowly and without obvious cause eight days before. The penis of the otherwise apparently healthy and well-nourished child was in sharp erection, firm, and two to three times its normal size. The veins were dilated, and a walnut-sized mass was palpable in the perineum. The inguinal lymph nodes were neither swollen nor tender. The bladder could be emptied readily, and the urine was normal. The priapism was not altered by either sleep or narcosis. After biopsy had revealed a malignant growth invading the perineal tissues, the penis, together with the mass, which had completely surrounded the urethra and involved the corpora cavernosa, was excised back to the pars membranacea. The wound healed well, but in a few weeks the child failed and died at home. There was no autopsy. The surgical specimen was 13 cm. in length and consisted in its distal two-thirds of the glans penis and corpora and proximally, of the tumor mass which had lain in the perineum. The mass on section was soft, and from it a grayish-white fluid could be expressed. The tumor compressed the urethra, invaded the surrounding tissue, and extended forward in the corpora cavernosa penis to the glans. The mucous membrane of the urethra throughout the length of the specimen was free, but its wall and the corpora cavernosa where they passed through the tumor were thickened and apparently infiltrated. Histologically the tumor consisted almost exclusively of round, oval, or polygonal cells with very little fine fibrous stroma.

8. Creite: Peniscarcinom bei einem 2 jährigen Kinde, Deutsche Ztschr. Chir. **79**:299, 1905.

The nuclei were large and vesicular with prominent nucleoli. The cells lay close together, forming broad bands, with occasional gland-like arrangement. No direct transition of endothelium into tumor cells could be demonstrated. The surface epithelial layer of the urethra was everywhere intact though elevated into mushroom-like projections by growth beneath. Creite, after a discussion of the facts, came to the conclusion that the growth was a cancer rather than an endothelioma, with a possible but not proved origin from Cowper's gland. As this tumor occurred in a young child, it seems extraordinary that the question of its possible origin from a Cohnheim rest was not mentioned. Schultze [9] in reviewing the case considered it an endothelioma.

A strikingly similar case and the only other example of this type of tumor occurring in a child was reported by Gobbi [10] from Rome, Italy, in 1922. It concerned a boy of 10 months who had a gradual swelling and enlargement of the penis over a period of 80 days. The case was referred by the village doctor to Professor Marchuetti in Modena. He observed an otherwise well-developed infant, somewhat thin, with a penis resembling an adult organ in erection. It was firm, and the increase in size was due to enlargement of the two cavernous bodies, while the corpus cavernosum urethrae did not appear involved and there was no difficulty of micturition. The prepuce covered the glans completely, but the skin was nowhere adherent. The left inguinal nodes appeared inflamed and fluctuant. The prepuce was incised and a biopsy specimen taken from an ulcerated area on the glans. The child went rapidly downhill and died a few days later. There was no autopsy.

Histological examination of the biopsy specimen revealed the tumor to be composed of large blood spaces filled with erythrocytes and surrounded by zones of neoplastic cells. These cells were very pleomorphic, tending to arrange themselves with nuclei perpendicular to the axis of the vessel in the closest layer and becoming more irregular where farther removed. Very narrow bands of collagenous fibers were interpolated between the anaplastic elements and the endothelial cells. The tumor cells were generally mononuclear, but occasional multinuclear forms occurred. The cytoplasm was homogenous or, sometimes, slightly granular. Mitoses were numerous. On the basis of his studies the author concluded that the tumor was primary in the corpus cavernosum and had originated from perithelial elements. The article is well illustrated.

In addition to the case of this tumor reported by Gobbi in a child, the Italian literature contains two cases in adults. Pelagatti [11] in 1910 described the case of a 65-year-old man who entered the hospital in severe uremia. The bladder was markedly distended. For a year the patient had experienced difficulty in urination and severe pain in the penis radiating to the perineum. On examination the penis was found to be in semierection, to be augmented in volume, and to have an irregular nodular surface. The glans was not covered but was swollen and congested, with an erythematous meatus. The skin covering the penis was free but

9. Schultze, W. H.: Männliche Geschlechtsorgane, in Brüning, H. and Schwalbe, E.: Handbuch der allgemeiner Pathologie und der pathologischen Anatomie des Kindesalters, Weisbaden, Germany, J. F. Bergmann, 1913, Vol. 2, p. 618.

10. Gobbi, L.: Contributo allo studio dei tumori endotheliali, Policlinico (sez. chir.) **29**:23, 1922.

11. Pelagatti, M.: Endothelioma dei corpi cavernosi del pene e dell' uretra, Dermat. Stud. **20**:318, 1910.

elevated by nodules, which pushed it up from below along the long axis of the organ. No metastases were demonstrated clinically. Catheterization was done without difficulty, but the patient died before an operation was performed. At autopsy the skin and tunica appeared uninvolved but the corpora were filled with a partly nodular, partly solid, compact, grayish, friable tissue. Microscopically this was found to be a neoplastic growth of large, pale-staining epithelial-like cells which lined or completely filled the cavernous spaces. In these spaces the lining endothelium had disappeared, but where the growth had extended into small veins and lymphatics it was still present. Arteries were apparently invaded only from without. Mitotic figures were numerous. The prostate was free. The author considered this tumor an endothelioma arising from the lining cells of the cavernous spaces.

Migliorini [12] in 1905 reported having examined a piece of tissue sent by a colleague and made a diagnosis of perivascular sarcoma of the penis. The patient was 50 years old. Clinical details of the case are wanting except that the tumor is known to have appeared first as a painless swellling in the glans a year and a half before and there was no enlargement of the lymph nodes. Although the fact is not clearly stated in the text, apparently the glans was excised. It was globular, hard, and cyanotic-reddish in color, but without ulceration. Histological sections revealed the cavernous spaces and vessels to be lined by large irregular sometimes multinucleated cells. A lumen was usually preserved, in which there were erythrocytes and amorphous material. Mitotic figures were numerous. About the larger spaces were smaller aborted vesicular channels, and the large number of newly formed vessels of various sizes and shapes was a most striking feature. The microscopic structure is well illustrated in an accompanying drawing and leaves little doubt as to the endotheliomatous character of the process.

Two examples of this tumor have been reported in the Japanese medical literature. Yamamoto [13] in 1930 described a rare case of priapism due to intravascular endothelioma. It concerned a farmer 58 years of age, who in December had injured his penis when a large crate of dried leaves toppled over on him. After the immediate effect of the trauma urination was painful for some time. In March a lump was noticed in the right side of the base of the penis, but this disappeared when he suddenly passed five clots of blood each about the size of a pea. In April the pain became more severe, the proximal part became purplish, and true priapism developed. In May the glans, uninvolved until now, became hard, there was phimosis, and urination was difficult. The patient was admitted to the hospital in July in a state of marked priapism. General examination revealed nothing of note. The inguinal nodes were slightly enlarged and the scrotum clear. The corpora cavernosa and glans were woody-hard, but the skin was purplish, soft, and edematous. Urination was difficult and followed by dribbling. To relieve the condition, which was believed due to a chronic cavernitis following a traumatic hematoma, a penectomy was performed. At operation it was noted that the corpora

12. Migliorini, G.: Contributo clinico ed istologico alla conoscenza dei sarcomi cutanei, Gior. ital. mal. ven. **40**:278, 445, 1905.

13. Yamamoto, K.: Ein seltener Fall vom Priapismus, insbesondere ein Beitrag zur Endothelioma intravasculare des Penis, Jap. J. Dermat. & Urol. **30**:420, 1930; Ein seltener Fall vom Priapismus, der durch Endothelioma intravasculare der corpora cavernosa penis erzengt wurde, ibid. **30**:50, 1930.

cavernosa were indurated, and bleeding was minimal. Pus containing staphylococci could be expressed from the stump. One month later the patient died from myocardial failure. There is no report of an autopsy. The surgical specimen was 13 cm. long, and 14 cm. in circumference and weighed 130 gm. The corpora were not of normal consistency, but the general architecture was well preserved. The urethral lumen was greatly narrowed. Histologically the cavernous spaces were found to be lined by layers of large cells with large vesicular nuclei and poorly defined cytoplasmic boundaries. Transition between the neoplastic cells and the endothelial lining of the spaces could be traced. There were no giant cells or evidence of glycogenic or fatty changes. There was no stroma except where the walls of the spaces had been invaded. Here the tumor cells tended to form vascular channels which contained blood. Mitotic figures were seen here and there. The mucous membrane of the urethra was free, but its cavernous tissue was infiltrated by growth. The arteries were empty but histologically normal, and the lymphatics were not involved. The veins, on the other hand, showed growth through their walls and tumor cells free in the lumen. Destruction of the cavernous tissue was most marked at the base of the penis, a fact which led to the belief that the neoplasm had originated in that region.

The second case from Japan was reported by Nagayo,[14] and reference to it is made in Yamamoto's paper. Details are lacking, and I was unable to obtain the original article. It concerned a 24-year-old man in whom a malignant tumor developed in the base of the penis at the site of the bulbous part of the urethra. A mass the size of an "eagle's egg" was present between the anus and the testes. It was excised, but growth extended into the bladder, rectum, regional nodes, muscle, and skin. Death occurred six months after the start of the illness. It was noted that giant cells due to fusion of the tumor cells and glycogenic changes were present. The author stated that the case resembled those of Maurer and Colmers.

Balog and Cerqua,[15] also in 1930, reported a case from the Italian Hospital in Cairo, Egypt. It concerned a robust Armenian, 40 years of age, whose past history was irrelevant except for gonorrhea 18 years before, which had healed without complications. In 1928 he had first noticed pain at the root of the penis and a very small nodule could be felt. The pain became progressively worse, particularly during erection, so that coitus was no longer possible, and the tumor had increased noticeably in size. On examination the penis was medium-sized, without any visible abnormality. However, palpation revealed a pea-sized, smooth, round nodule at the root near the anterior surface and somewhat to the left. The skin was freely movable over the tumor, which, however, was firmly attached to the underlying tissues. The urethra and inguinal nodes were free. At operation the tumor was found to lie in the left corpus cavernosum and to be well encapsulated. It was excised intact, and the patient was able to leave the hospital in 10 days. No recurrence had appeared at the end of five months. Histologically the parenchymal tumor cells varied considerably in size and shape as well as in arrangement. Some cells formed canal-like structures, while others were irregularly placed in the fibrous stroma. The cells were sometimes large and polygonal, with large, round, vesicular nuclei; dark nucleoli and foamy cytoplasm were observed. In several areas the

14. Nagayo, M.: Dr. Muira Moriji, 25th Anniversary Volume of Collected Papers.

15. Balog, P., and Cerqua, S.: Endothelium des Corpus cavernosum penis, Arch. Dermat. u. Syph. **161**:86, 1930.

characteristic appearance of a capillary angioma was encountered. The stroma sprang from the fibrous capsule and showed as thick bundles which narrowed down and lost themselves between the parenchymal cells. Mitoses were wanting, and elastic fibers were not demonstrable within the capsule. The capillaries of the stroma possessed a normal-appearing endothelium. They were for the most part empty, but several of the channels lined by tumor cells were filled with blood. The authors considered the lesion comparable in its slow growth, complete encapsulation, and curability by excision to those previously reported by Alexander and Dunham and by Hildebrand. The article is well illustrated.

In a paper on the application of urethrography, Dobrzaniecki [16] in the same year described a somewhat similar, apparently benign endothelioma observed at the surgical clinic of the University of Lwow. His patient, a man of 59, had first noticed a year before admission that the urinary stream diverged to the left. Micturition became difficult and was followed by pain, though there was neither hematuria nor purulent discharge. The patient said that he had never had a venereal disease. The penis appeared normal, but palpation showed infiltration of the inferior portion of the glans and extension backward, although without sharp limitation into the corpora cavernosa. The scrotum and its contents were apparently not affected. The inguinal glands were slightly enlarged, but soft. Rectal examination showed the prostate to be considerably enlarged and firm. During passage of a very fine bougie the inferior surface of the navicular fossa was found to be extremely firm, but its upper part was soft. Urethrography revealed an irregular contour of the urethra and constriction. Moreover, the opaque liquid passed through its wall into the surrounding tissues. The distal third of the penis was amputated and the inguinal glands excised. Four months later there was no evidence of recurrence. Splitting of the specimen along the sagittal axis revealed marked constriction of the urethra in the glans and below a grayish-yellow mass, which was sharply defined from the surrounding tissues with destruction of the corpora cavernosa. The structure was composed of inflammatory tissue and believed to be secondary to the tumor below. The latter consisted of pleomorphic endothelial cells which lined spaces and in arrangement resembled clusters of grapes. The author believed the growth to have arisen from the lining of the large blood spaces. The histological description leaves much to be desired, but a photomicrograph shows a typical endothelioma.

A case in Canada was reported in 1938 by Foulds and Flett [17] of Toronto. The patient, who was a groom 46 years of age, was admitted to the Toronto General Hospital in 1923. He gave a history of semi-invalidism following influenza the previous year but no urogenital trouble up to that time. Around the border of the glans penis there was an indurated reddish tender area, and the induration extended back along the whole length of the corpus cavernosum urethrae as a hard nodular cord. The corpora cavernosa penis and inguinal nodes were apparently free. Films of the spine showed localized rarefaction in the body of the third lumbar vertebra. A diagnosis of carcinoma of the urethra with metastases to the spine was made. There is no record of treatment. Over five years later the patient was

16. Dobrzaniecki, W.: L'endothéliome de la verge et l'application de l'urétrographie, J. urol., Paris **29**:368, 1930.

17. Foulds, G. S., and Flett, R. H.: Endothelioma of the Corpora Cavernosa, J. Urol. **40**:826, 1938.

admitted to St. Michael's Hospital in serious condition due to pain, weakness, cough, and shortness of breath. The glans penis was hard. The corpus cavernosum urethrae was a mass of firm irregular nodules which extended back to the prostate and also were present in the corpora cavernosa penis. The left seminal vesicle was firm and palpable, and the third lumbar vertebra was collapsed. He died three weeks later. At autopsy the penis was semierect. The mucous membrane of the urethra was intact throughout, and cross section of the penis showed an unaltered anatomical arrangement. Throughout the cavernous tissue of the penis and urethra there were firm grayish areas containing multiple minute hemorrhagic spots. A firm nodule surrounded the bulbous portion of the urethra. The regional lymph glands were not involved. Metastases were present in the lungs, liver, spleen, kidneys, and brain and presumably in the lumbar vertebra. The outstanding histological feature was the presence of masses of tumor cells filling or partially filling the cavernous spaces and also present within the blood vessels of the fibrous trabeculae of the tunica and of the subcutaneous areolar tissue. The cells varied in appearance but were mostly polyhedral, with clear cytoplasm and a large nucleus. In the center of the larger masses there was considerable fatty degeneration. A peculiar hyaline fusion of the cells with loss of cytoplasmic boundaries had occurred. The cells seemed to arrange themselves into capillary-like channels and lined spaces containing blood. Little fibrous stroma or inflammatory reaction was encountered.

The most recent case to be reported in the medical literature was by Coppridge, Putnam, and Miale[18] in 1946 from the Lincoln Hospital in Durham, N. C. A 58-year-old Negro was admitted because of swelling and pain in the penis. Nine months previously he had noticed a nodule on the corona, which was thought by his local physician to be a primary syphilitic lesion; this had apparently responded to antisyphilitic therapy. Three weeks prior to admission he had visited another clinic, at which time a hard bluish nodule 1 cm. in diameter was present in the right side of the corona, accompanied by considerable balanoposthitis. The prepuce was slit and a biopsy specimen taken from the tumor. There were no abnormal physical findings except those of the genitalia. The glans measured 10 cm. in diameter and was edematous and acutely inflamed, with ulceration. The inguinal nodes were tender but not fixed to the skin, and there was no priapism. After clearing up of the infection a biopsy specimen was taken from the penis and an inguinal node was excised. During the manipulation of the penis the glans came away with blunt dissection. About two weeks later the penis was amputated 5 cm. proximal to the main lesion. Postoperatively the patient received 2,400 r to the inguinal region and stump. Five months later he seemed well, with no evidence of recurrence. There is no further follow-up. The tumor was faintly lobulated, pale gray, and rubbery and involved the corpora cavernosa up to the site of amputation. The urethra was surrounded, but its mucosa appeared free. Histologically the pattern of the tumor was pseudoalveolar, with thin delicate fibrous septa forming the framework for the large polygonal cells with clear cytoplasm which lined the spaces. Mitotic figures were present, and there were erythrocytes in the spaces. In some areas the spaces were collapsed and the tumor appeared more cellular. The lymph nodes were inflamed but did not show any metastases. The lesion was considered an endothelioma.

18. Coppridge, W. M.; Putnam, G. H., and Miale, J. B.: Endothelioma of the Penis, J. Urol. **56**:112, 1946.

REPORT OF CASES

CASE 1.—On Oct. 3, 1948, A. McG., aged 53, was admitted to the surgical service of Dr. A. L. Wilkie at the Royal Victoria Hospital for herniorrhaphy. During the physical examination a small, tender, firm bean-shaped tumor was noted in the left lateral region at the base of the penis. This was considered to be a Peyronie plaque and was removed by Dr. Allan B. Hawthorne. The report of the operation was as follows: "A longitudinal incision was made over the mass. This hard cartilaginous calcified area was in the sheath of the corpora cavernosa. The mass was excised. The edges of the sheath were then sutured together to stop the bleeding from the venous sinuses." Subsequent questioning of the patient furnished no information as to the duration of the lesion. He made an uneventful recovery and was free from recurrence three years later.

The specimen sent to the pathological laboratories consisted of a firm-to-rubbery mass of light-brownish tissue the size of a large bean. Histological sections of the whole specimen show it to be limited peripherally by the thick wall of the tunica albuginea, while elsewhere it was surrounded by a thin fibrous membrane. In the part of the tunica adjacent to the lesion there were many large dilated venous channels. The encapsulated area was obviously the seat of a vascular neoplasm, which varied considerably in appearance in different places. Where most highly differentiated and organized it was composed of small well-formed closely packed vascular channels lined by flat endothelial cells with little supporting stroma. The nuclei were long and narrow, with compact chromatin. The structure was here essentially that of a capillary hemangioma. However, such areas were sparse and small, and at the peripheries of them the endothelial cells gradually increased in size, with a greater amount of cytoplasm and larger, oval or circular, vesicular nuclei. The vascular arrangement was preserved, but as the endothelial cells enlarged the spaces tended to widen until they simulated those of erectile tissue. Eventually the tumor cells reached considerable size, with abundant eosinophilic cytoplasm, very large nuclei, and prominent nucleoli. Some cells were apparently fused into syncytial masses without cytoplasmic boundaries. Here vascular arrangement was practically lost in a sponge-like meshwork of strands and cords. The little supporting tissue consisted of a mixture of smooth muscle and fine collagenous fibrous connective tissue. Many of the channels were filled with blood, and there was considerable iron-staining pigment. No mitotic figures could be demonstrated. The lesion was looked upon as a hemangioendothelioma arising in the corpus cavernosum and, in view of the sparsity of mitotic figures and absence of any invasion of the capsule, was considered benign.

CASE 2.—L. P., a steward aged 75, entered the service of Dr. Emerson Smith at the Royal Victoria Hospital on Oct. 24, 1950. He gave a history that 10 days before, while lifting a case, he had experienced a sudden sharp pain above the root of the penis. This lasted an hour and then passed off, leaving a tender area. The following day the organ began to swell, at first dorsally about midway down the shaft. The lump increased in size for a few days and then became relatively static. Except for some symptoms obviously referable to prostatism, the history was otherwise negative. Physical examination showed the patient to be well preserved for his age. The prostate had a Grade II hypertrophy and was firm, rubbery, smooth, symmetrical, and not tender. The penis had a semierect appearance and was indurated, swollen, and slightly tender from the glans to a point just proximal to the symphysis. Beyond this area, both in the glans and in the root of the organ, the swelling markedly diminished. The testes and urethra were normal, and the regional nodes were not enlarged. Laboratory tests showed a nonprotein nitrogen value of 29.3 cc. per 100 ml. and a creatinine value of 1.15 mg. per 100 ml. The Wassermann reaction was negative and kidney function not impaired, but red blood cells were found in the urine (2+). A hemogram revealed a slight anemia with a sedimentation velocity of 17 mm. an hour. A leucocytosis, with a count of 10,400, was due to an increase in neutrophiles, eosinophiles, and lymphocytes. On Oct. 27 a tourniquet was applied to the penis and the right corpus incised. There was no evidence of thrombosis. The surgeon stated that the corpus was very dense and did not have the appearance of carcinoma. The biopsy specimen consisted of a small triangular piece of tissue, one side of which was firm and fibrous.

Histological sections showed a thick fibrous collagenous membrane, obviously the tunica albuginea, beneath which was the spongy tissue of the corpus cavernosum. The fibromuscular septa appeared relatively normal, but an extraordinary transformation, with filling up of the

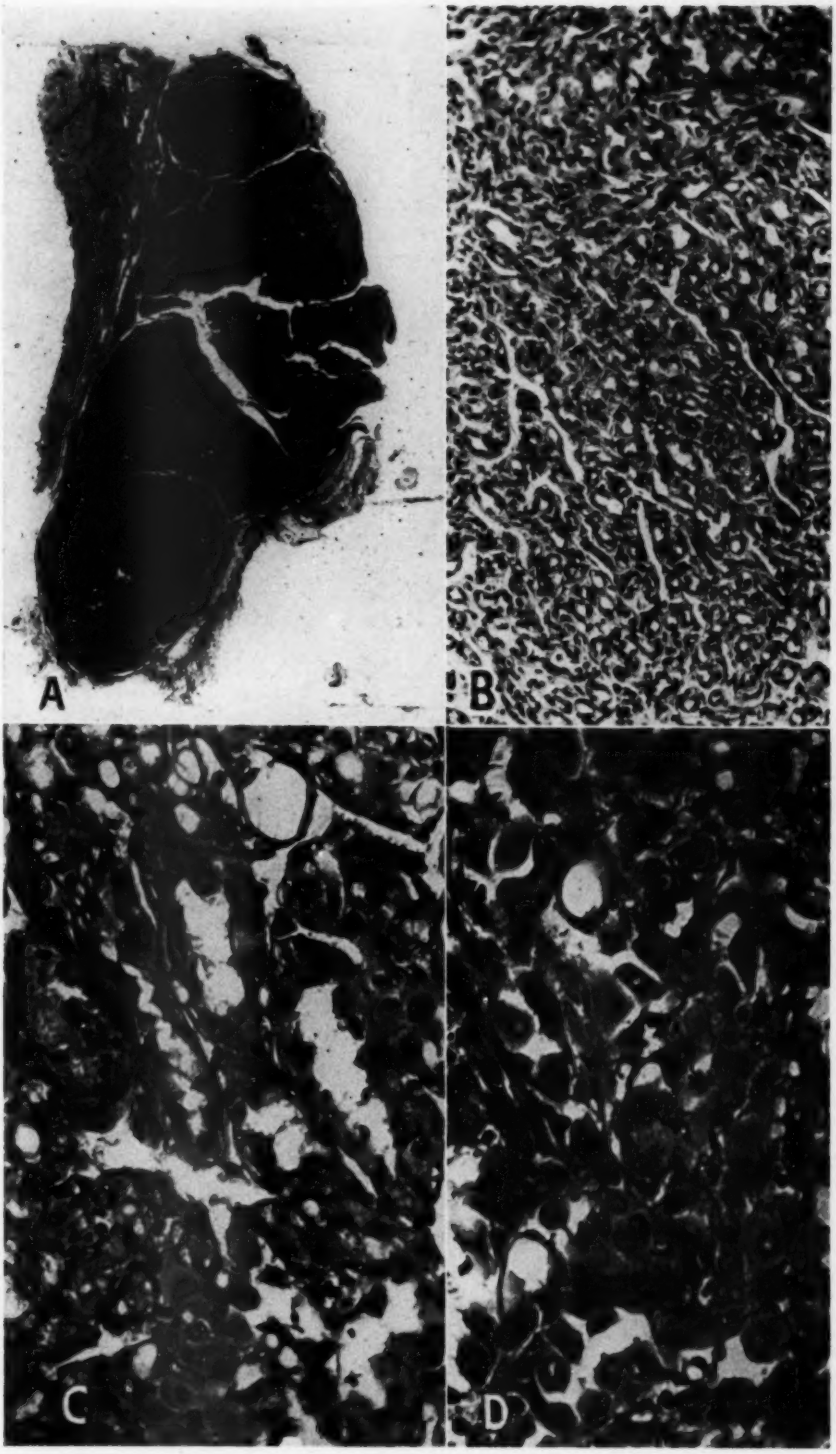

Fig. 1 (Case 1).—*A*, section of whole tumor (× 6); excised portion of tunica albuginea to the left and thin capsule to the right. Note coarse lobulation. *B*, area of typical capillary hemangiomatous structure (× 190). *C*, channels are here widened and lining cells larger, with abundant eosinophilic cytoplasm and prominent nucleoli in vesicular nuclei (× 410). *D*, solider area, with vascular structure only faintly preserved (× 410).

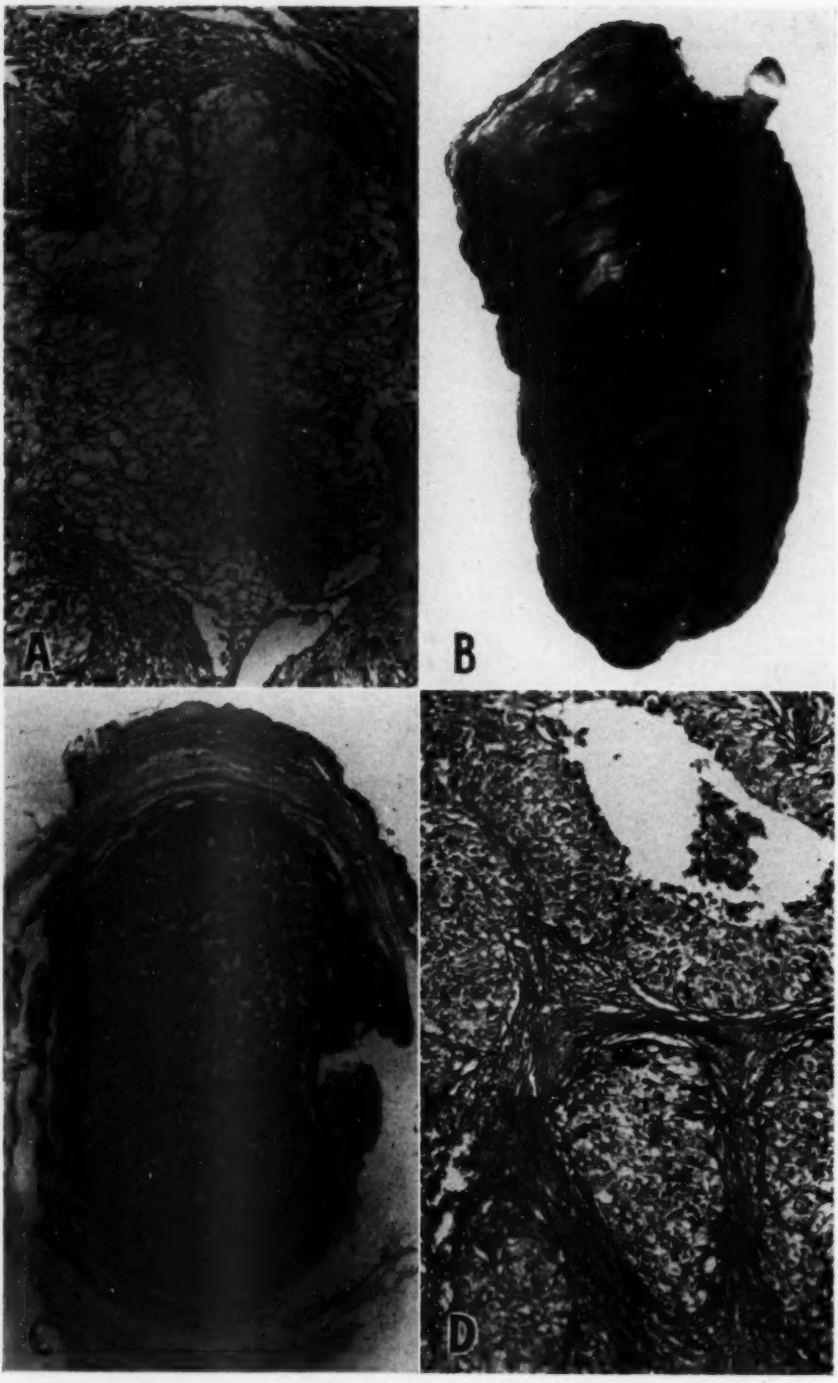

Fig. 2 (Case 2).—*A*, biopsy specimen (×90) showing cavernous spaces filled by large pale-staining polyhedral cells; mononuclear exudate in septa. *B*, amputated portion of penis, 9 cm. long and widened to 4.5 cm. at proximal end. *C*, topographical section of penis at point of amputation (× 3). Growth fills spaces of corpora cavernosa and corpus spongiosum. *D*, higher magnification, showing growth in spaces while septa are relatively free (× 83).

vascular spaces, had occurred. This consisted of a proliferation of fibroblastic elements, some lymphocytic and plasma cell infiltration, and endothelial budding, with formation of small vascular channels. These changes had led to recanalization in some places. The endothelial cells were often large and anaplastic and here and there formed large sheets and clusters of neoplastic tissue. No actual invasion of the septa, however, by these cells could be demonstrated. The endothelial cells were large pale-staining elements with vesicular nuclei, but mitotic figures were not noticeable. Some of the recanalized spaces were infiltrated with red blood cells, while others were free. Examination of the sections led to a diagnosis of endothelioma. It was concluded that the neoplastic process, if not already malignant, was at least potentially so. The extraordinary formation of granulation tissue within the spaces brought up the question as to whether the endotheliomatous tumor formation might not have been secondary and superimposed on an original fibrous and vascular tissue reaction.

The patient received a course of roentgen therapy, 2,900 r over a period of three weeks. It was terminated because the skin over the treated area would no longer tolerate radiation. No objective improvement in the size of the penis had occurred, and it was believed this fact indicated a radioresistent type of tumor. He was then discharged from the hospital. Three months later he returned, as he was having considerable difficulty in urinating, due partly to the condition of his penis and partly to a large prostate. Apparently extension of the growth into the root of the organ had occurred, but there were no palpable nodes. His lung fields were clear. A permanent suprapubic cystostomy and bilateral vasectomy were done on Feb. 23. There was no evidence of invasion of the growth into the retropubic space or over the prostatic capsule, and he was discharged on March 19.

On May 16 the patient was readmitted. He was suffering considerable pain in the distal portion of the penis and becoming somewhat anemic from loss of blood in the urine; however, there was no evidence of general decline in his condition. Some extension of the growth had occurred, but the regional nodes were not enlarged. A partial amputation was carried out about 1 in. from the root. There was evidence of tumor tissue in the remaining stump, and the medial septum was distorted. The specimen consisted of the distal portion of the penis. It was 9 cm. long and widened to 4.5 cm. at its proximal end. It was firm and hard, with some phimosis. Large topographical sections of the proximal end of the amputated portion showed the general structural arrangment to be well preserved. The tunica was thickened, and the septa of the erectile tissue were widened by an increase in collagenous fibers. Every cavernous space, however, was occupied to a greater or lesser extent by tumor cells. These might simply rim the space, replacing the endothelial lining by several layers of the neoplastic elements, with blood in the remaining lumen, or they might completely obliterate it. Where a lumen was present, it sometimes appeared to have been relined by regenerated flat endothelial cells. Invasion of the septa was rarely observed, but there was a distinct tendency for the growth to follow vascular channels and thus appear in the wall of the tunica. The growth extended into the spaces of the corpus cavernosum urethrae in similar manner but the lining mucosa of the urethra was free. Considerable edema and a variable amount of mononuclear exudate were found in the septa, and large quantities of brownish pigment, which gave a positive reaction for iron, were present in histiocytes or free in intercellular spaces. The tumor cells were large, flat, polygonal elements with well-defined cytoplasmic boundaries that joined closely together, forming a solid sheet. The nuclei were vesicular, large, and round or oval, with prominent nucleoli. The cytoplasm was abundant and either was clear or showed a faint-staining gossamer meshwork. Where a lumen was maintained within the mantle of growth it often contained broken-down erythrocytes and desquamated necrosing tumor cells. These cells often contained a brownish pigment in clumps or fine granules. Similar pigmentation was occasionally found in the cells of the surrounding layer. The pigmentation might suggest a melanotic tumor, but we were unable to demonstrate any pigment that did not stain for iron, and Fontana stains were negative. Mitotic figures were present but not numerous.

Although there was still some discharge from the wound, the patient returned to his home on the 17th postoperative day. Three months later he returned to the hospital; in the interval he had remained well. Examination, however, showed that the growth had extended into the inguinal nodes, and there was a firm, fixed, tender mass halfway down the anterior aspect

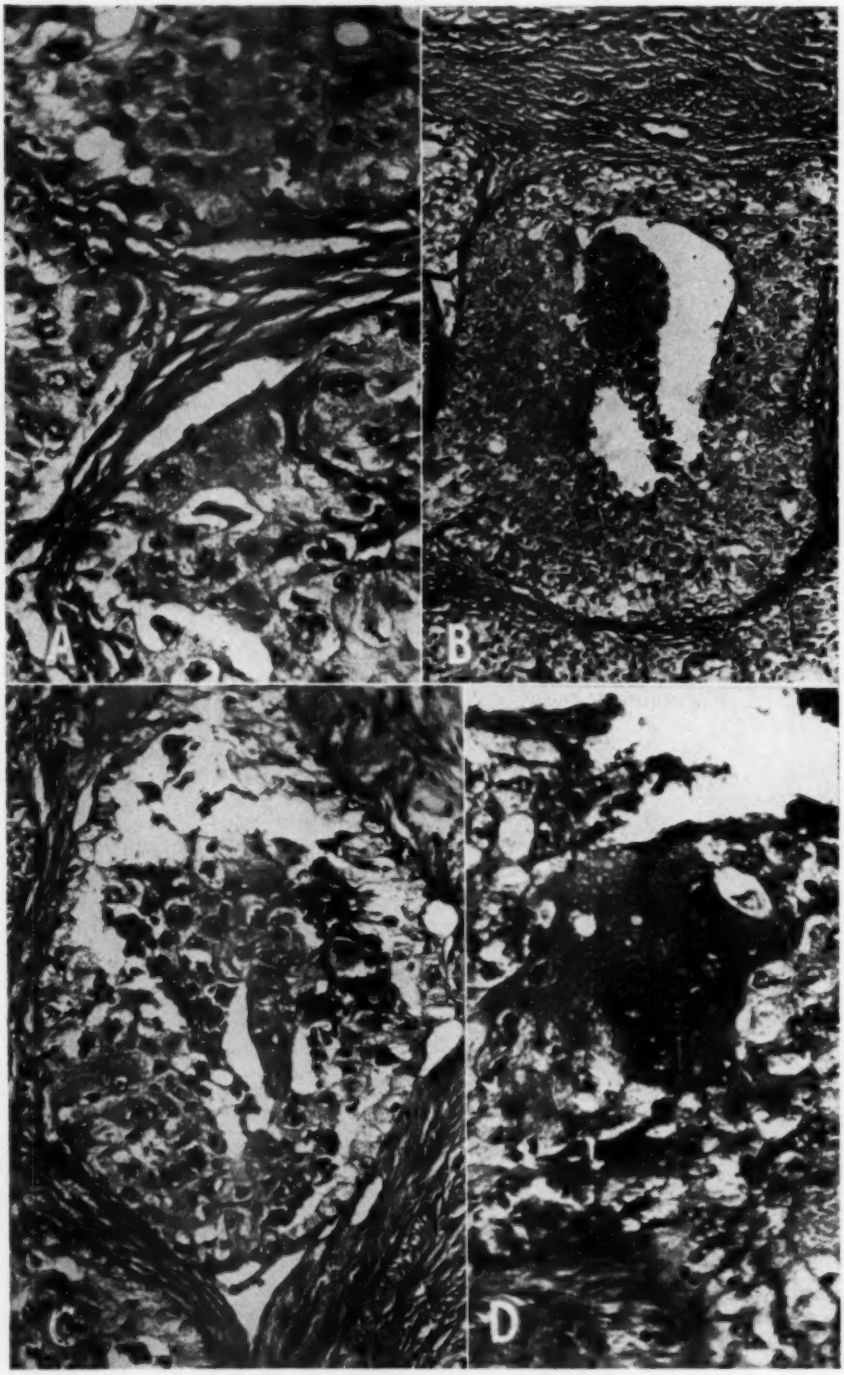

Fig. 3 (Case 2).—*A*, spaces filled by practically solid sheets of large polygonal cells (× 380). *B*, lumen preserved and containing erythrocytes and fragments of cell detritus (× 87). *C*, darker-staining cells in center are filled with iron-containing pigment (× 170). *D*, fusion of tumor elements into large multinucleated giant cell (× 390).

of the femur, in its middle third. The pelvic bones and chest were free. After fulguration of granulation tissue on the stump of the penis, he was allowed to return home. His family physician reported that he died about three months later. No autopsy was performed.

ANALYSES OF CASES

An analysis of the 16 cases of endothelioma of the corpora cavernosa of the penis would appear to justify a division into three distinct groups. To emphasize this difference, the tumors have been designated endothelioma infantum, endothelioma benignum, and endothelioma malignum, respectively.

The cases reported by Creite and by Gobbi occurred in infants and were strikingly similar in their rapidly progressing malignant course. In them the precise classification and source of origin are naturally more difficult to determine and remain controversial. At this age period, however, one is inclined to favor the probability that the growth has originated on the basis of some developmental defect in the laying down of the cavernous tissue of the organ. Of the remaining 14 examples of this disease, including our own, there was evidence in 5 of a circumscribed lesion and benign course with no recurrence following excision, while

TABLE 1.—*Endothelioma Infantum*

Author	Age of Patient	Signs and Symptoms	Duration	Treatment	Outcome	Autopsy	Pathological Diagnosis
Creite (1905)	2 yr.	Erection; dilated veins; mass in perineum	8 d.	Amputation to pars membranacea	Death after 2½ mo.	No	Malignant; author's diagnosis—cancer (Cowper's gland?); Schultze—endothelioma
Gobbi (1922)	10 mo.	Erection due to enlargement of corpora cavernosa of penis; urethra free	8 d.	Biopsy of ulcer on glans	Death within few days	No	Malignant; origin in corpus from perithelial elements

in the other 9, malignancy and rapid progress of the disease were for the most part conspicuous features. Ewing [19] has already called attention to this apparent difference in the behavior of such tumors.

The average age of the five patients with the benign type was 54 years. The known duration was apparently about a year, and the patient complained of painful erection or micturition. A small lump was found beneath the tunica, involving the erectile tissue, while the skin was free. In Hildebrand's case the tumor originated in the corpus spongiosum, while in that reported by Dobrzaniecki the origin was in the glans. There appeared to be no tendency to recur following excision. The first example in this group, described by Alexander and Dunham, while its signs, symptoms and course were typically benign, was considered by Professor Dunham, who carried out the pathological studies, as malignant. We attempted to obtain histological sections of the lesion for review but were unsuccessful. There is some discrepancy. The surgeon stated that the tumor was "not encapsulated," but histologically it was reported as having "at the surface, a dense, perhaps incomplete, fibrous capsule." However, some of the tumor cells are described as presenting mitotic figures, and the tumor was believed to be growing rapidly. It is apparently impossible to settle the question from the evidence at hand.

19. Ewing, J.: Neoplastic Disease: A Treatise on Tumors, Ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 373.

The average age of the nine patients with malignant disease was 53 years. Five patients were in the fifties, noticeable exceptions being Nagayo's patient, who was 24, and our patient of 75. To the best of our knowledge no similar tumors have ever been reported in the erectile tissue of the clitoris. The known duration is usually less than six months. However, in the case reported by Foulds and Flett the patient was suspected of having a carcinoma of the urethra with metastases to a lumbar vertebra five years previously. Painful semierection with marked hardening and swelling is the usual complaint. A definite nodule may be palpable, or the lesion may have infiltrated most of the organ, with metastases to the inguinal nodes. A history of apparent onset following trauma or exertion was present in two cases. One patient showed signs of a hematoma. Excision or amputation was performed in six cases. In the two most recent cases the patients also had radiation therapy. Seven patients are known to have died within weeks or months. Of the

TABLE 2.—*Endothelioma Benignum*

Author	Age of Patient	Signs and Symptoms	Duration	Treatment	Outcome	Autopsy	Pathological Diagnosis
Alexander and Dunham (1897)	50 yr.	Penis curved on erection; painless lump on dorsum	6 mo.	Excision	No recurrence within 27 mo.; patient died after 3 yr. (cause?)	No	Malignant endothelioma
Hildebrand (1906)	68 yr.	Dribbling; hard lump on under surface	1 yr.	Extirpation of mass	No recurrence within 6 mo.	...	Endothelioma intravasculare arising in corpus cavernosum urethrae
Balog and Cerqua (1930)	40 yr.	Painful erection; pea-sized nodule in root	2 yr.	Excision	No recurrence within 5 mo.	...	Benign, encapsulated endothelioma
Dobrzaniecki (1930)	59 yr.	Painful micturition; mass in glans	1 yr.	Amputation	No recurrence within 4 mo.	...	Circumscribed endothelioma
Waugh (1952)	53 yr.	Tender, firm, bean-sized nodule in lateral aspect near base	?	Excision	No recurrence within 3 yr.	...	Endothelioma benignum

others, Migliorini's patient had no follow-up and Dr. Coppridge has informed us that he and his associates were unable to trace their patient after five months.

Analysis of the series from the histopathological point of view reveals that the benign tumors are small, localized, and circumscribed if not actually encapsulated lesions. In Hildebrand's case the tumor cells lined the cavernous spaces, with orientation which they tended to lose as they piled up and degenerated toward the center of the lumen. Balog and Cerqua called attention to capillary hemangiomatous areas, and such areas were present in our specimen. In fact, a gradual enlarging of the lining cells of small capillary channels, with eventual loss of vascular structure and haphazard arrangement, was a striking feature. Eventually, extremely large polygonal elements with large vesicular nuclei and abundant, finely granular cytoplasm dominate the picture. There is a scanty, finely collagenous supporting stroma. Mitotic figures are not found.

In the malignant form there is no evidence of a circumscribed mass of neoplastic tissue or areas of benign capillary hemangiomatous structure. The tumor cells line, encircle with a mantle, or completely fill the cavernous spaces. The normal flattened endothelial surface cells of the large vascular channels are for the most part wanting. Where the tumor cells rest against the wall there is only slight orientation, and

even here they are large and anaplastic. Mitotic figures are present, but not numerous. The cells show a tendency to form large, flat-appearing, polygonal elements with fairly well-defined borders of the finely granular cytoplasm. The nuclei are often very large, round or oval, and vesicular, with fine chromatin mesh and usually one, but sometimes even two or three, prominent nucleoli. There is very little stroma. Where a lumen in the space remains, it contains erythrocytes and desquamated and degenerating tumor cells. These phagocytose blood pigment, and there is considerable hemosiderin in the septa. Invasion of the walls is not a

TABLE 3.—*Endothelioma Malignum*

Author	Age of Patient	Signs and Symptoms	Duration	Treatment	Outcome	Autopsy	Pathological Diagnosis
Maurer (1883)	50 yr.	Lumps in inguinal region; penis hard and half erect	3 mo.	None	Death in 1 mo.	Yes	Endothelioma intravasculare; widespread skin metastases
Colmers (1903)	56 yr.	Painful erection; firm nodules and lymph vessels	2 mo.	Amputation	Death 1 wk. postoperatively	Yes	Endothelioma arising from corpora cavernosa; widespread metastases
Migliorini (1906)	50 yr.	Painless swelling of glans	1½ yr.	Excision ?	No follow-up	...	Perivascular sarcoma (illustrations suggest endothelioma)
Pelagatti (1910)	65 yr.	Severe uremia; penis semierect, nodular	1 yr.	Catheterization only	Death within 1 wk.	Yes	Endothelioma from lining cells of cavernous spaces; invasion of vascular channels
Yamamoto (1930)	58 yr.	History of trauma and hematoma; hardening of corpora and glans	6 mo.	Amputation	Death 1 mo. postoperatively (myocardial failure)	No	Endothelioma intravasculare with invasion of veins; origin from base of penis
Nagayo	24 yr.	Mass in base of penis at site of bulbous urethra	6 mo.	Excision	Death 6 mo. after start of illness	Yes	Growth in bladder, rectum, regional nodes, etc.; author stated case resembled those of Maurer and Colmers
Foulds and Flett (1938)	46 yr.	Extensive involvement of penis with widespread metastases	5 yr.	None	Death 3 wk. after admission	Yes	Malignant endothelioma of corpus cavernosum; urethra free; metastases to liver, lungs, brain, etc.
Coppridge, Putnam, and Miale (1946)	58 yr.	Nodule on corona, with inflamed glans	9 mo.	Amputation and irradiation	No recurrence within 5 mo.	...	Endothelioma; urethra free; growth in corpora cavernosa to amputation site
Waugh (1962)	75 yr.	Sharp pain at root following exertion; semierect, swollen, and tender penis from glans to symphysis	10 d.	Biopsy, irradiation, and amputation	Death 14 mo after 1st admission	No	Endothelioma malignum; metastases to inguinal nodes and left femur

conspicuous feature, but growth along the lumina of veins is frequently encountered. The presence of glycogen in the neoplastic elements has been reported in some cases. Extension into the root of the penis is a tendency, with lymphatic metastases first appearing in the inguinal nodes. In the case reported by Maurer and in one of the two reported here, spread occurred down the leg and into the femur. In four of the five cases which came to autopsy there are records of widespread metastases.

COMMENT

The question naturally arises as to whether one is justified in considering these tumors as endotheliomata. As each of the three groups presents particular features it would seem advisable to take them up separately.

In both of the two cases occurring in infants there was considerable doubt as to the origin of the malignant cells. Creite described glandular arrangement and was inclined to look upon the tumor as a cancer with possible origin from Cowper's gland. Schultze, however, later reviewed the material and considered the tumor an endothelioma. As to the other case, reported by Gobbi, there is no apparent reason for doubt that the tumor was primary in the corpora cavernosa; however, he described narrow bands of collagenous fibers interpolated between the anaplastic elements and the lining cells of the spaces and came to the conclusion that, while the tumor was endothelial, the source of the growth was perithelial elements. Both of these cases are old ones, and until another example of this infantile neoplasm occurs and is subjected to careful study it would seem impossible to arrive at any positive conclusions.

In the benign group, the cases reported by Balog and Cerqua and the case here reported in which typical capillary hemangiomatous areas were present leave little doubt as to their endotheliomatous nature. It may well be, however, that such tumors arise not from the actual lining cells of the erectile tissue but rather through a peculiar proliferative activity and transformation of the endothelium of a small quiescent vascular neoplasm. The growth, with alteration in the appearance of these cells, is most extraordinary and by no means a common finding in the usual hemangiomata. The fact that these tumors occur in the penis might raise the question of their belonging in the category of the so-called benign adenomatoid tumors of the genital sphere, which have been shown by Masson, Riopelle, and Simard [20] to be of celomic derivation and hence mesotheliomata. However, their location in the corpora cavernosa, in contrast to the epididymis, is against their origin from peritoneal serosa, and my example, at least, lacked the distinctive structural and cytological features of the mesotheliomata. The diagnosis in Hildebrand's case led to considerable controversy. His conclusion that the tumor was an endothelioma intravasculare was criticized by Borrmann, who believed it to be a urethral cancer, and by Colmers, who raised the question of origin from the endothelial lining of lymph spaces. On the basis of the description it seems difficult to accept Borrmann's view. It is quite possible that not all the tumors included in this group are essentially the same.

On the other hand, the histological features of the tumors in the third, or malignant, group conform closely to a uniform type and have many common characteristics. They first appear within the tunica albuginea; they tend to line, mantle, and fill the cavernous spaces, with replacement of the endothelium; they have very little stroma and rarely invade the septa except to grow within the lumina of veins. The cells are flat polygonal elements forming sheets. Their nuclei are large, vesicular, round or often oval, with one or more prominent nucleoli. Mitotic figures are present but scarce, considering the rapidity of growth. There is no suggestion of gland formation or squamous cell characteristics.

The possibility that these are metastatic growths from an unrecognized primary carcinoma elsewhere in the body has to be considered. This view is tenaciously held by those who believe that the endothelial lining of vascular spaces is incapable of forming such malignant neoplasm. Certainly it is an uncommon lesion; however,

20. Masson, P.; Riopelle, J. L., and Simard, L. C.: Le mésothéliome bénin de la sphère génitale, Rev. canad. biol. **1**:720-751, 1942.

if these tumors were secondary, all their peculiarities would have to be explained by the fact that the metastatic carcinoma had given up its natural attributes and, because of its location in the corpora cavernosa, had taken on different cytological structure and manner of growth. This possibility is difficult to conceive.

Metastasis of carcinoma to the erectile tissue of the penis can undoubtedly occur. Begg [21] has reported a case in a man aged 62 who complained of persistent priapism. At autopsy a cystic and a solid growth were found in the kidney, with nodules in the liver and involvement of the corpora cavernosa. The author was careful to point out that the microscopic appearance of the tumor was distinctly that of a renal carcinoma with masses of cubical cells having an elongated acinar arrangement, strongly resembling the convoluted tubules of the kidney. This fact excluded the possibility that the lesion in the penis was the primary site. Moreover, Frontz,[22] at the meeting of the American Association of Genito-Urinary Surgeons in 1927, described the findings in a case of priapism due to malignancy. Postmortem examination revealed involvement of the penis, prostate, and bladder and widespread distant metastases. The primary site was not determined. In the discussion of this paper, Alcock mentioned a similar case in which the pathologists disagreed as to the exact nature and origin of the malignant growth.

In the nine cases of malignant disease in adults outlined here, postmortem examinations were done in five. Of these, four showed widespread metastases in the body, but in Pelagatti's case there was apparently no extension except into the local vascular channels.

As time goes on pathologists become more and more hesitant about attributing the origin of tumors to the lining of vascular channels. Such an origin is often difficult if not impossible to prove. However, there is no doubt that these tumors of the penis have several striking and characteristic features in their manner of growth and cellular structure that distinguished them from carcinoma and sarcomata and strongly suggest their origin from endothelium. The cases in this group are both clinically and pathologically strikingly similar and constitute a distinct entity of disease.

CONCLUSIONS

The 16 recorded cases of endothelioma of the corpora cavernosa of the penis, including two here contributed, have been reviewed. The salient features, both clinical and pathological, of the series have been discussed and summarized. On the basis of this analysis a division into three groups, designated as endothelioma infantum, endothelioma benignum, and endothelioma malignum, has been proposed.

21. Begg, R. C.: Persistent Priapism Due to Secondary Carcinoma in the Corpora Cavernosa, Brit. M. J. **2**:10, 1928.

22. Frontz, W. A., and Alyea, E. P.: Priapism of Unusual Etiology: Case Report, Tr. Am. A. Genito-Urin. Surgeons **20**:315, 1927.

OBSERVATIONS ON NATURE OF GALACTOSE TOXICITY IN RATS

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THE PRESENT studies were initiated in an attempt to clarify the nature and mechanism of reported bone changes as well as the general nature of the toxicity of galactose. Mason and Turner [1] and Goldbloom and Brickman [2] reported cases of galactosemia in which osteoporosis was detectable by roentgenological examination; however, no histological bony changes in humans have been reported. Handler [3] reported osteoporosis in rats fed diets containing lactose and galactose. Again, this observation was based on roentgenologic examination.

METHODS

Weanling rats of the Wistar strain, 21 days old, were placed in individual cages and given food and water ad libitum. The diet consisted of casein 18%, galactose 70%, peanut oil 8%, calcium carbonate 1%, potassium dihydrogen phosphate 2%, salt mixture 1%, and a vitamin mixture.[4] The control animals were given a similar diet in which glucose was substituted for the galactose. The animals were weighed daily, and their food intake was measured similarly. The animals were placed in metabolism cages for collection of urine and feces for certain short-term balance experiments.

Calcium and phosphorus balance studies were carried out as follows: Analysis was made for each animal of the pooled feces which had been collected daily over the entire metabolic period. The daily 24-hour urine specimens were analyzed individually. The calcium analyses were performed by the Shohl and Pedley method [5] and the phosphorus analyses by the Fiske and Subbarow method.[6] The nitrogen determinations were made on aliquots of the digested feces and of urine by Kjeldahl microdetermination. The values for amino-acid excretion were obtained by the method of Folin,[7] and the amounts of fermentable reducing substances were estimated by the method given by Peters and Van Slyke.[8]

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From the Department of Pathology, the Department of Nutritional Research, and The Children's Cancer Research Foundation of The Children's Medical Center.

1. Mason, H. H., and Turner, M. E.: Am. J. Dis. Child. **50**:359, 1935.
2. Goldbloom, A., and Brickman, H. F.: J. Pediat. **28**:674, 1946.
3. Handler, P.: J. Nutrition **33**:221, 1947.
4. The salt mixture and vitamin mixture were those used by Wolbach and Maddock (Wolbach, S. B., and Maddock, C. L.: A. M. A. Arch. Path. **53**:273, 1952).
5. Shohl, A. T., and Pedley, F. G.: J. Biol. Chem. **50**:537, 1922.
6. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**:375, 1925.
7. Folin, O.: Laboratory Manual of Biological Chemistry with Supplement, Ed. 5, New York, Appleton-Century-Crofts, Inc., 1934.
8. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. 2, Baltimore, Williams & Wilkins Company, 1932.

At postmortem examination, the organs were weighed, and the tissues were fixed in Zenker's acetic acid solution, formalin, and absolute alcohol for glycogen studies. The tissues fixed in absolute alcohol as well as tissues from the eyes were embedded in celloidin.

RESULTS

Clinical Observations.—The galactose-fed animals gained weight steadily but slowly; their total average weight gain at the end of 75 to 78 days was but 50 to 60% of that of the control animals. They were active and ate well, their total food intake, for example, being 153% of that of the control animals after 10 days and 125% after 72 days on the diet. The urine volume of the galactose-fed animals after 40 days on the diet was about 70 cc. a day in contrast to the 16 cc. a day of the control animals. Daily ophthalmoscopic examination revealed that the earliest peripheral lens opacities could be detected by the 9th day, and dense central opacities were first seen on the 13th day of the diet. The latter were present in all the galactose-fed animals by the 20th day. By the 16th day, definite corneal vascularization of an even, diffuse nature was present in these animals. This occurred without

TABLE 1.—*Calcium and Phosphorus Balance Studies: Values for Twenty-Four-Hour Period*

		Calcium					Phosphorus				
			Output, Mg.		Balance			Output, Mg.		Balance	
Diet Period	Food Intake, Gm.	Intake, Mg.	Urinary	Fecal	Mg.	% of Intake	Intake, Mg.	Urinary	Fecal	Mg.	% of Intake
11th to 19th day											
Galactose-fed rats*	11.2 (10.5-12.0)	48.3 (45.1-51.5)	1.93 (1.03-2.67)	10.58	35.89	74.4	44.3 (41.6-47.5)	25.1 (23.5-27.4)	3.4	15.8	35.6
Glucose-fed rats†	7.3 (5.5-10.0)	46.4 (34.9-63.4)	1.03 (0.54-2.38)	10.28	32.57	70.2	45.1 (33.9-61.7)	16.6 (13.9-22.4)	3.3	25.3	56.2
70th to 75th day											
Galactose-fed rats†	18.5 (17-19.8)	117.4 (107.9-125.6)	....	40.93	.....	>60.0	114.2 (104.9-122.1)	74.6 (69-84)	20.8	18.8	16.5
Glucose-fed rats†	14.6 (13.9-17.8)	92.7 (80.8-112.8)	6.95 (1.71-14.58)	29.57	57.55	62.2	90.1 (78.6-109.1)	46.7 (44.2-63.5)	10.8	31.3	34.8

* Diet contained 0.43% calcium and 0.40% phosphorus.
† Diet contained 0.64% calcium and 0.62% phosphorus.

any gross evidence of opacity or scarring of the surface of the cornea. None of these features developed in the glucose-fed controls.

Metabolic Studies.—Calcium and phosphorus balance studies were carried out from the 11th to the 19th day and from the 70th to the 75th day of the diet with two different pairs of animals. The values obtained in a sample experiment are shown in Table 1. As can be seen from this table, positive balances were obtained for both calcium and phosphorus in the galactose-fed animals. Moreover, these occurred even when the galactose-fed animals were maintained on a diet containing two-thirds as much calcium and phosphate as the diet given the glucose-fed controls. The urinary phosphorus outputs were increased in the galactose-fed animals, but the fecal outputs remained the same. The increased urinary phosphorus output could be explained in part by an increased intake due to increased food intake. The control animals retained a considerably greater portion of their ingested phosphorus, as indeed they did of their entire caloric intake. The serum phosphorus values for the galactose-fed and glucose-fed control animals were not significantly different, 8 mg. per 100 cc. (range 7.3 to 10.2 mg.) for the galactose-fed animals and 7.7 mg. per 100 cc. (range 6.5 to 9.2 mg.) for the controls. The calcium

levels were also closely parallel, though only two values were obtained for each group, 8.6 mg. per 100 cc. (8.4 and 8.8 mg.) for the galactose-fed animals and 9.9 mg. per 100 cc. (9.8 and 10.0 mg.) for the controls.

The total-nitrogen excretion values of two pairs of galactose-fed and glucose-fed animals were determined by four-day collections of the urine and feces, from the 6th to the 10th and the 19th to the 24th day for the first pair, and from the 13th to the 17th day for the second pair. These are recorded in Table 2. It is there revealed that the urinary nitrogen excretions of the galactose-fed animals were as much as three times those of the controls for the period when the animals were receiving an almost equivalent total food intake. When computed on a weight basis,

TABLE 2.—*Nitrogen Balance Studies: Values for Twenty-Four-Hour Period*

			Food		Nitrogen				
							Output, Mg.		
Diet Period	Diet	Body Weight, Gm.	Intake, Gm.	Intake, Gm. per 100 Gm. Body Weight	Intake, Mg.	Intake, Mg. per 100 Gm. Body Weight	Fecal	Urinary	Balance, Mg.
6th to 10th day*	Galactose	62.6	9.4	15	271	433	10	186	75
	Glucose	78.0	10.2	12	293	345	10	63	220
19th to 20th day*	Galactose	85.0	14.2	18	409	519	16	203	190
	Glucose	152.0	15.2	10	438	288	11	169	258
13th to 17th day	Galactose	50.8	11.1	18.5	319	551	16	191	112
	Glucose	137.5	8.0	11	230	168	10	57	163

* These values were obtained from the same pair of animals.

TABLE 3.—*Amino-Acid Excretion: Values for Twenty-Four-Hour Period*

Diet	Average Body Weight, Gm.	Food Intake, Gm.	Amino-Acid Nitrogen Excreted, Mg.	Amino-Acid Nitrogen Excreted in Urine, Mg. per 100 Gm. of Body Weight
Galactose-fed rats	137 (122-140)	18.1 (17-19.8)	2.88 (2.46-3.65)	2.16 (1.98-2.60)
Glucose-fed rats	265 (263-274)	14.2 (13.9-17.8)	2.16 (2.02-2.21)	0.8 (0.82-0.83)

these values are more striking, the galactose-fed animals excreting two to four times as much nitrogen in the urine as the control-fed animals.

The urinary excretion of amino-acid nitrogen also was increased in the animals on the galactose diet, though this moiety obviously represented but a small fraction of the total nitrogen excreted. These values were obtained from an average of five 24-hour urine specimens obtained from the 74th to the 79th day on the diet. The food intake of the galactose-fed animals averaged 120% of that of the glucose-fed animals during this period. The average total excretion value was 2.88 mg. of amino-nitrogen per 24 hours (range 2.46 to 3.65 mg.) for the galactose-fed animals against 2.16 mg. per 24 hours (range 2.02 to 2.21 mg.) for the glucose-fed rats. The difference is more striking when presented on a body-weight basis (Table 3).

The urine was collected from paired animals from the 71st to the 75th day; it was concentrated *in vacuo*, and aliquots were used in paper partition chromatog-

raphy.[9] Serial dilution chromatograms showed that galactose-fed animals excreted a preponderant amount of the amino acids in peptide form rather than as free amino acids. The peptides were detected as slow-moving spots upon being sprayed with ninhydrin. After hydrolysis of the same aliquots with six times normal hydrochloric acid, these slow-moving spots were shown to resolve into individual amino acids, indicating that they were actually peptides. Hydrolyzed aliquots of concentrated urine, partially freed of salts, were used for formol titration, according to the method of Sorensen, and the results indicated that galactose-fed animals excreted an increased amount of amino-nitrogen a day in comparison with the glucose-fed rats. Thus, in the galactose-fed rats, the amino-nitrogen excretion was 25 mg. per 24 hours against 6.43 mg. per 24 hours for the glucose-fed animals.

Tryptophane was isolated from the urine of galactose-fed rats after hydrolysis with four times normal sulfuric acid, by precipitation as the mercuric sulfate complex, according to Lugg's method.[10] The tryptophane was separated from the complex by removing the mercury as mercuric chloride and was estimated colorimetrically with Ehrlich's reagent. It was thus found that the isolated tryptophane accounted for about 15% of the total amino-nitrogen of the hydrolyzed urine. This would mean that the amount of tryptophane (measured as tryptophane) excreted daily by the galactose-fed rat is about 27 mg. The dietary intake of these rats during the period of urine collection averaged 20 gm. a day. The tryptophane content of this amount of diet would be approximately 50 mg., so that on this limited protein intake, nearly 50% of the tryptophane is lost directly in the urine as amino acid in a peptide linkage and perhaps also free. Additional losses would be expected to occur in the catabolism of the tryptophane of the diets, since galactose-fed animals also excrete a much higher percentage of their ingested nitrogen than do glucose-fed control animals.

Since it has been reported that in rats fed a tryptophane-deficient diet cataracts develop in a short time, as well as vascularization of the cornea,[11] both these changes being present in our galactose-fed animals, and since our animals lost in the urine a high percentage of their ingested tryptophane, the galactose diet was supplemented with added tryptophane in an effort to determine whether the formation of cataracts could be delayed or inhibited by the addition of a single amino acid. Tryptophane was added to the diet at levels of 2% and 0.2%. The animals receiving the larger amount failed to eat and did not gain weight as well as the galactose-fed controls, whose diet was not supplemented with tryptophane. At neither level was the formation of cataracts delayed beyond the time at which they occurred in the galactose-fed rats which did not receive added tryptophane in their diets. The diet of these animals was not continued for a sufficient time for us to determine whether or not corneal vascularization would develop.

Examination of the urine of the galactose-fed and control glucose-fed rats for fermentable reducing substances gave negative results in both instances. Thus, it is apparent that, although large amounts of galactose are excreted by galactose-fed animals, no glucose appears in the urine at levels detectable by this method.

9. The estimations of the peptide excretion, the chromatographic analyses, and the isolation of tryptophane were performed by Dr. L. L. Uzman.

10. Lugg, J. W. H.: Biochem. J. **31**:1423, 1938.

11. (*a*) Schaeffer, A. J., and Murray, J. D.: Arch. Ophth. **43**:202, 1950. (*b*) Totter, J. R., and Day, P. L.: J. Nutrition **24**:159, 1942.

Pathologic Observations.—Six galactose-fed and seven glucose-fed control animals were maintained on their respective diets for 75 to 78 days. At the end of this time, they were killed and examined. Microscopic examination of the tissues was carried out.

After this period on the diet, the galactose-fed animals were well groomed and active. They were much smaller than the control animals (Table 4). At the beginning of the experiment the average weights were 39 and 41 gm., respectively. Diffuse vascularization was present uniformly over the corneas in these animals, but no roughening or scarring of the corneas was evident. The change in the corneas was no longer recognizable after the circulation ceased at death. The galactose-fed animals had no depot of subcutaneous fat.

Postmortem roentgenologic studies revealed no gross differences in the structure or density of the bones in the galactose-fed and control glucose-fed rats. On the average, the livers weighed less in the galactose-fed animals. However, these animals had no lack of Best's-carmine-positive material within the liver parenchyma; this compared in amount to that seen in the glucose-fed controls. No evidence of liver fat infiltration was found in either galactose-fed or glucose-fed animals. Samples of the alcohol-fixed celloidin-embedded liver material were stained with iodine, aqueous toluidine blue, eosin, and Best's carmine stain before and after digestion with saliva

TABLE 4.—*Postmortem Data**

Diet	Body Weight, Gm.	Weight of Liver, Gm.	Weight of Kidney, Gm.	Kidney Weight in % of Body Weight	Weight of Testis, Gm.
6 galactose-fed rats	131 (94-154)	6.9 (5.4-8.7)	0.86 (0.690-1.05)	0.66	0.62 (0.28-0.712)
7 glucose-fed rats	263 (132-354)	13.1 (6.8-14)	0.96 (0.8-1.1)	0.31	1.43 (1.2-1.5)

* Figures are average values; the range is given in parentheses.

and malt diastase according to the schema of Grainger and Shillitoe.[12] These authors stated that this battery of procedures could differentiate between glycogen and galactogen. With iodine staining, marked differences in reactivity of the liver cell deposits were noted. The liver cells from the glucose-fed animals showed widespread positive staining in the iodine-stained sections, equivalent to the staining in sections stained with Best's carmine. Among the galactose-fed animals, however, almost no positive reaction for glycogen was obtained after staining with iodine, though much Best's-carmine-positive material was present. Digestion with saliva or 2% malt diastase in buffer solution removed the Best's-carmine-positive material from the livers of both glucose-fed and galactose-fed animals.

The kidneys of the galactose-fed and glucose-fed animals weighed nearly equal amounts (Table 4). Those of the former were enlarged and definitely hydronephrotic (Fig. 1). On a kidney-weight/body-weight ratio the kidneys of the galactose-fed rats were much larger, the average ratio being 0.66% for the galactose-fed rats against 0.31% for the glucose-fed control animals. The only recognizable histological abnormalities found associated with this increase in mass were rather uniform but small deposits of Best's-carmine-positive material in the loops of Henle in the kidney tubules of the galactose-fed animals.

12. Grainger, J. N. R., and Shillitoe, A. J.: Stain Technol. **27**:81, 1952.

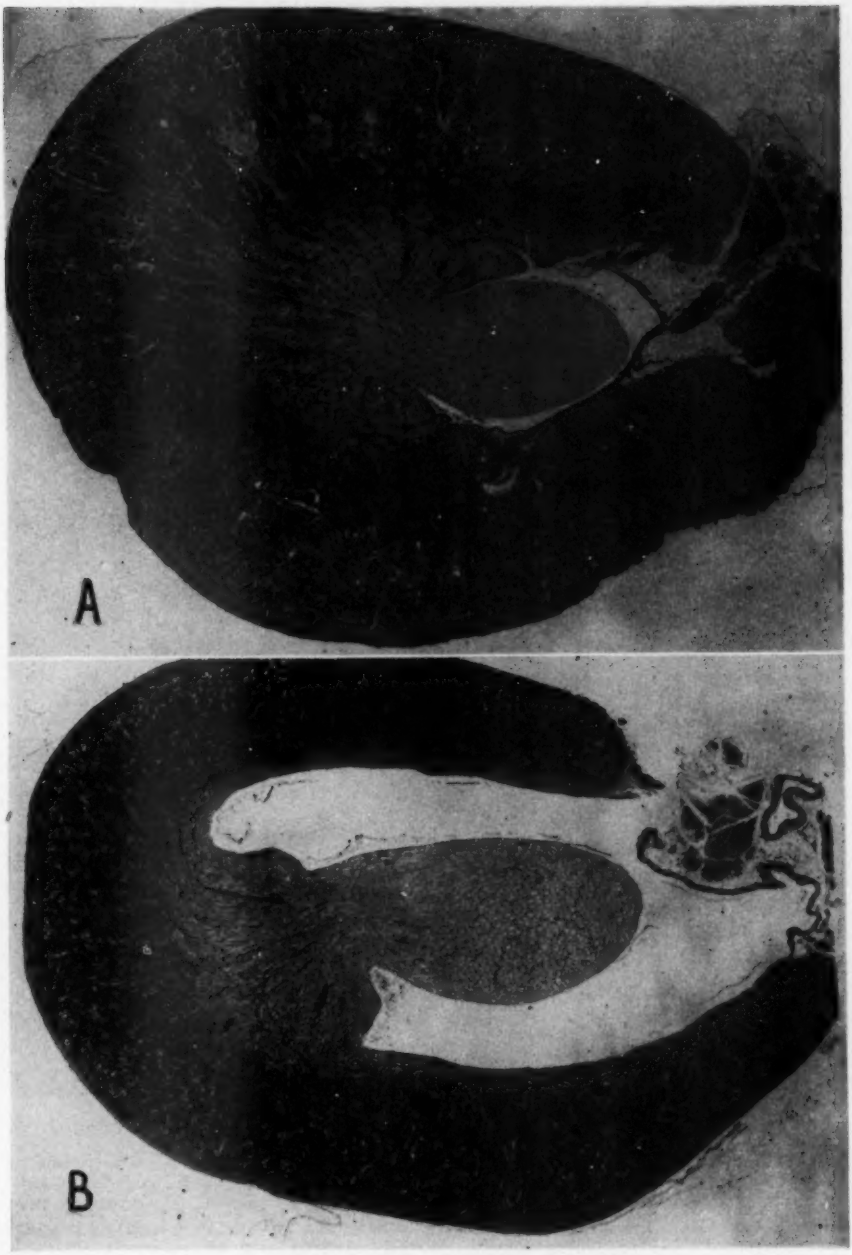

Fig. 1.—*A*, kidney from control glucose-fed rat. (Hematoxylin and eosin, × 15.) *B*, kidney from galactose-fed rat. Considerable dilation of the pelvis is present. (Hematoxylin and eosin, × 15.)

The adrenals of the galactose-fed animals had absolute weights equivalent to those of the controls. There was slight, but not uniform, hyperplasia of the glomerulosa zone. The testes of the galactose-fed animals showed a variable degree of atrophy (Fig. 2, *A* and *B*), their average weight being 0.62 gm. against 1.43 gm. for the controls. They showed considerable irregular atrophy of the tubules,

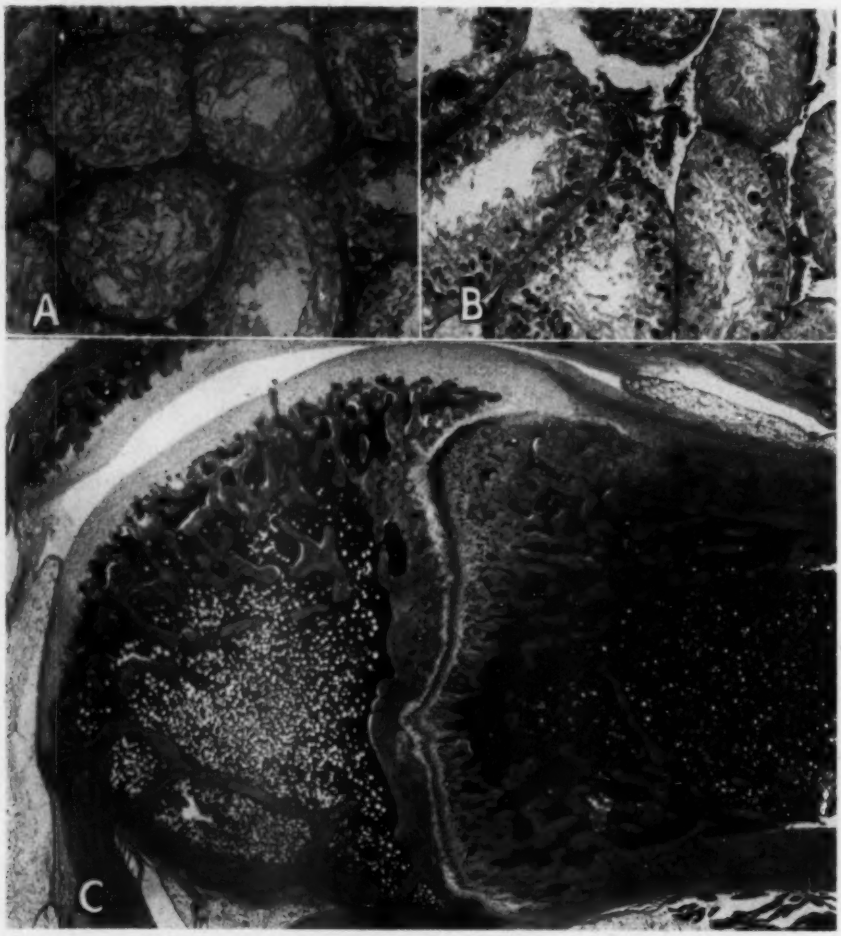

Fig. 2.—*A*, testis from galactose-fed rat. Marked atrophy of seminiferous tubules is present, with apparent hypertrophy and hyperplasia of interstitial cells. (Hematoxylin and eosin, × 120.) *B*, testis from galactose-fed rat. Less severe atrophy of tubules is present. Interstitial cells are prominent. (Hematoxylin and eosin, × 120.) *C*, tibia from 99-day-old galactose-fed rat. No defects in bone formation or structure are present. (Hematoxylin and eosin, × 8.)

with varying degrees of arrest of sperm maturation, ranging to complete loss of spermatogenic cells and often of the Sertoli elements. The shrinkage of the tubules in the extreme cases often gave rise to an apparent increase in the interstitial ele-

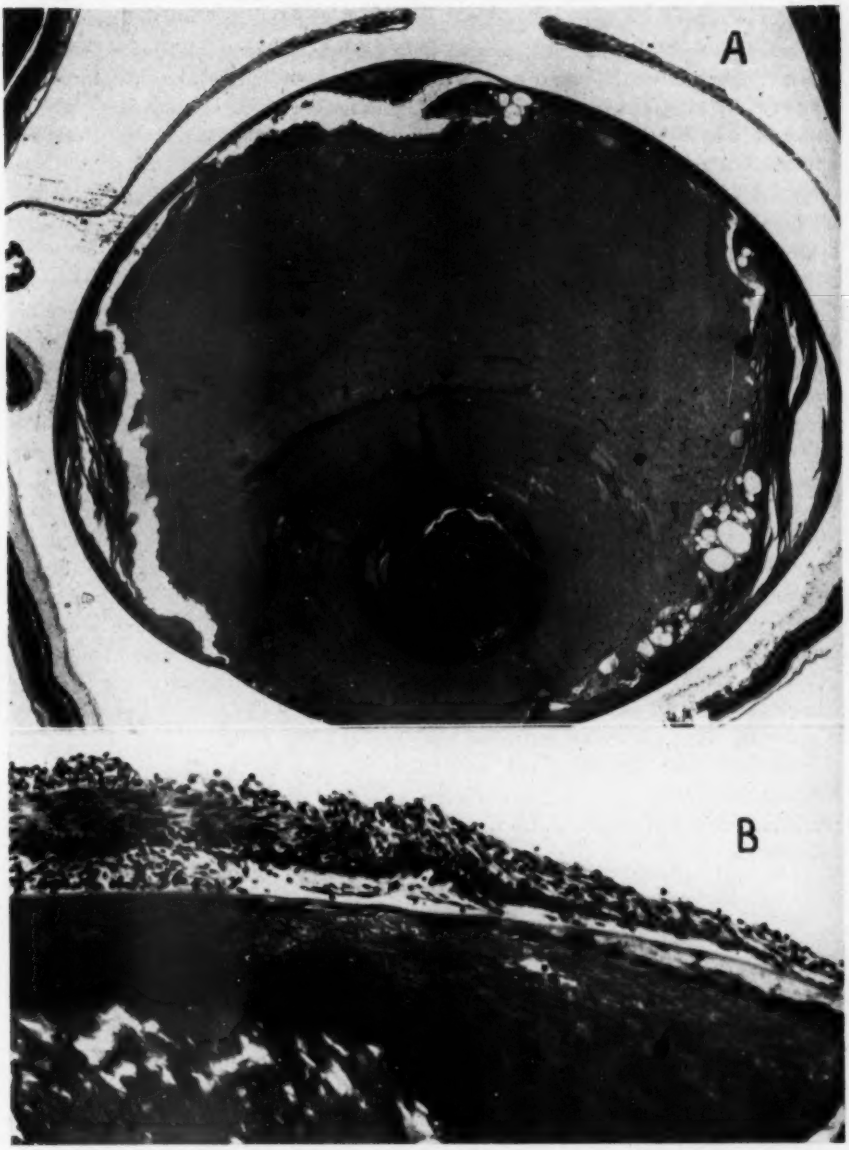

Fig. 3.—*A*, lens from galactose-fed rat. The nuclear remnant has been displaced posteriorly. It is lying in a coagulated structureless protein material. At anterior edge of lens capsule, a mass of proliferating fibroblasts can be seen. (Hematoxylin and eosin, × 29.) *B*, lens and iris diaphragm from galactose-fed rat. There are adhesion and inflammation of iris and lens capsule. A small group of proliferating fibroblasts is present in lens capsule at extreme right. (Hematoxylin and eosin, × 200.)

ments. No thickening of the tubular basement membranes was present. The bladders of the galactose-fed animals were dilated. The prostatic tissue of the galactose-fed animals was much reduced in size and weight, the average weight being 0.62 gm. against 0.93 gm. for the controls. Atrophy of the prostatic epithelium was present. The seminal vesicles of the galactose-fed animals were much smaller than those of the controls, but no significant histological changes were encountered in the epithelium.

Sections of tibia and femur showed no recognizable alteration in the endochondral bone formation or the trabecular pattern (Fig. 2*C*). The hematopoietic elements appeared normal.

Sections of the eyes of the galactose-fed animals showed a dense central remnant of the formed lens surrounded by a loose, edematous, unorganized protein precipitate (Fig. 3*A*). At the periphery of the lens, beneath the capsule, large balloon cells were present, which increased in size as they progressed toward the center of the lens. They did not lose their cytoplasmic boundaries as in a normal lens. These cells eventually enlarged to the point of rupture and dissolution. Anterior synechiae were present, with inflammatory thickening of the iris diaphragm in three animals of the galactose-fed group. In these, also, an inflammation of the aqueous humor was present, and free-lying inflammatory cells, chiefly polymorphonuclear and mononuclear, were persent in the anterior chamber. Microscopically, it was difficult to recognize capillary loops in the corneal segments; they were extremely small and appeared to consist of single endothelial cells lining a tiny space. No inflammation of the cornea was present. In five of the six galactose-fed animals there was proliferation of fibroblasts at the anterior lens capsule, frequently at the area of adhesion of the iris diaphragm (Fig. 3*B*). These cells invaded the substance of the lens. In one or two instances, considerable collagen had been laid down by the proliferating fibroblasts. Best's carmine stain for glycogen and the Sudan 4 stain for fat on alcohol-fixed and formalin-fixed specimens revealed no significant differences between the eyes of the two groups in the deposition of either glycogen or sudanophilic material. No abnormalities were found in the sections of the eyes of glucose-fed animals.

COMMENT

In our experiments, neither the serum levels, the balance data on calcium and phosphorus metabolism, the postmortem roentgenologic survey, nor histological sections of the bones revealed any significant deviation from normal in the formation or structure of the bone. The ash content of the femurs of rats fed galactose over a period of several weeks has been reported to be normal.[13] Hernberg[14] reported that on roentgenologic examination, the bony structure in alloxan-treated diabetic rats is more gracile-appearing than is that of normal rats, but that the histological features of the diabetic and control rat bones have no distinguishing elements. He attributed the roentgenologic appearance to the decreased nitrogen available for bone matrix formation in the diabetic rats. Reports by Handler[3] of osteoporosis, which were based on roentgenograms of galactose-fed animals, may have resulted from a similar appearance. The high excretion values for the available nitrogen in our

13. Mitchell, H. S., and Dodge, W. M.: J. Nutrition **9**:37, 1935.

14. Hernberg, C. A.: Acta med. scandinav. **142**:274, 1952.

galactose-fed animals and their limited protein intakes suggest that inadequacy of available protein may have given a picture of osteomalacia in Handler's rats.

The high excretion of peptide and amino-nitrogen by the galactose-fed rats, with retention of but a relatively small portion of the ingested protein, is in line with the atrophic changes in the testis and the failure of growth and development of the visceral organs. The development of corneal vascularization as a late phenomenon has been attributed to a variety of protein and amino-acid deficiencies.[15] The amino acids involved include phenylalanine, tryptophane, leucine, isoleucine, methionine, arginine, histidine, threonine, and valine. The formation of cataracts in amino-acid deficiency appears also to result from deficiencies of any of the indispensable amino acids except arginine.[16] It has been suggested that when the growth of the animal is severely depressed, cataract formation due to amino-acid deficiency will not take place.[11b] Cataracts have been experimentally induced also by various other means, including xylose feeding,[17] induced diabetes,[18] riboflavin deficiency,[19] hypoparathyroidism,[20] and feeding thallium [21] or naphthalene.[22] Naphthalene is in effect a metabolic antagonist of cysteine, since the latter is utilized in its detoxification.[23] It may be of interest to point out here that Holzel and his associates [24] reported that infants with galactosemia and early cataract formation, who were on a milk diet, excreted amino acids in abnormal amounts; tryptophane was not among the amino acids which they identified in the urine. On a galactose-free diet, these infants had a normal excretion pattern.

The failure of added tryptophane alone to delay or prevent the development of cataracts in galactose-fed rats on a protein-restricted diet is not surprising, since deficiencies of other indispensable amino acids may also have been present. Since histidine is also excreted in large quantities, along with tryptophane, by human diabetics under poor control,[25] it may be that this amino acid was also in deficient supply in our animals. Moreover, the excretion data indicate that a high proportion of the ingested nitrogen was excreted in the urine, and competition may have existed between the requirements of intrinsic body protein formation and the catabolism of ingested protein for energy requirements, so that a general protein deficiency existed; the control glucose-fed animals grew rapidly on a similar protein intake. The increased protein metabolic demand probably arises as a result of the comparatively low glucose values in the peripheral blood, values of the true glucose levels running between 23 and 73 mg. per 100 cc., as reported by Handler,[3] in galactose-

15. Sydenstricker, V. P.; Hall, W. K.; Bowles, L. L., and Schmidt, H. L., Jr.: J. Nutrition **34**:481, 1947.

16. Hall, W. K.; Bowles, L. L.; Sydenstricker, V. P., and Schmidt, H. L., Jr.: J. Nutrition **36**:277, 1948.

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18. Chaikoff, I. L., and Lachman, G. S.: Proc. Soc. Exper. Biol. & Med. **31**:237, 1933.

19. Day, P. L.; Darby, W. J., and Langston, W. C.: J. Nutrition **13**:389, 1937.

20. Erdheim, J.: Mitt. Grenzgeb. Med. u. Chir. **16**:632, 1906.

21. Buschke, A.: Arch. Dermat. u. Syph. **116**:477, 1913.

22. Goldmann, H.: Klin. Monatsbl. Augenh. **83**:433, 1929.

23. Bourne, M. C., and Young, L.: Biochem. J. **28**:803, 1934.

24. Holzel, A.; Komrower, G. M., and Wilson, V. K.: Brit. M. J. **1**:194, 1952.

25. Frankl, W.; Martin, H., and Dunn, M. S.: Arch. Biochem. **13**:103, 1947.

fed animals. Such a condition would evoke increased gluconeogenesis from the body and ingested protein. The increased incidence of cataract formation with high levels of carbohydrate intake and excretion in pancreatectomized and alloxan-treated diabetic rats suggests a similar mechanism in those animals. In both experimental diabetic [26] and galactose-fed rats,[27] the same factor of a high-protein or high-fat diet serves to delay or inhibit cataract formation. Charalampous and Hegsted [26a] showed that the time required for the onset of cataracts in alloxan-treated diabetic rats was inversely proportional to the amount of glycosuria of the animals. This varied greatly with diet and was abolished with a high-fat diet, which was completely protective, though the animals did not grow. Patterson [28] refined these observations and found that there was a lower limit of blood sugar at which no cataracts would occur, but above this value the time relation was inversely proportional to the blood sugar. He stated that this lower limiting value seemed to be related to the threshold value of the kidney for glucose. Since galactose has no threshold level,[29] one would expect a much lower blood level of this to be effective in the production of cataracts. Patterson suggested that the saturation of the renal threshold by sugar inhibits the resorption of essential amino acid by the tubules. The active role of the renal tubules in this regard may be seen in the tubular resorption of 98% of an intravenous dose of tryptophane in normal dogs.[30] Added to this factor of amino-acid and peptide excretion, for which we have elicited some evidence, is the increased catabolism of protein by the galactose-fed rats in comparison with the glucose-fed control animals. This factor may account for the formation of cataracts in Charalampous and Hegsted's galactose-fed, alloxan-treated diabetic rats when they were excreting 0.5 gm. a day of galactose in comparison with minimal cataract-producing excretion values of 27 gm. a day for the glucose-fed diabetic rats.

At postmortem examination of our galactose-fed animals, no recognizable histological abnormalities were present in the liver. The livers from these rats contained material which reacted with Best's carmine stain for glycogen, but only a minimum of the same material reacted with iodine; sections from the glucose-fed animals reacted to both iodine and Best's carmine stain. Such a reaction is said to be typical for galactogen. A chemical difference between "galactogen" and glycogen based on the number of free end-groups has been suggested [31] and denied.[32] It seems difficult to reconcile the adequate levels of apparent glycogen in the liver with a low fermentable sugar value in the peripheral blood, as reported by Handler.[3] The existence of a "galactogen" consisting of a polymer of galactose molecules would be credible in such a situation, yet there is little evidence for the existence of such a compound.

26. (*a*) Charalampous, F. C., and Hegsted, D. M.: Am. J. Physiol. **161**:540, 1950. (*b*) Rodriguez, R. R., and Krehl, W. A.: Yale J. Biol. & Med. **24**:103, 1951.

27. Mitchell, H. S., and Cook, G. M.: Arch. Ophth. **19**:22, 1938.

28. Patterson, J. W.: Am. J. Physiol. **165**:61, 1951.

29. Folin, O., and Berglund, H.: J. Biol. Chem. **51**:213, 1922. Harding, V. J., and Grant, G. A.: J. Biol. Chem. **99**:629, 1933.

30. Beyer, K. H.; Wright, L. D.; Russo, H. F.; Skeggs, H. R., and Patch, E. A.: Am. J. Physiol. **146**:330, 1946.

31. Bell, D. J.: Biochem. J. **30**:1612, 1936.

32. Schlamowitz, M.: J. Biol. Chem. **188**:145, 1951.

Deuel and his associates [33] presented data which show that the liver glycogen formed in galactose-maintained animals is more resistant to depletion and starvation than that formed in glucose-maintained animals. Unfortunately, he did not determine blood sugar, urine sugar, or nitrogen excretion in these animals to rule out other factors, such as gluconeogenesis from body protein stored in galactose-fed animals. This difference in resistance was not apparent in acute experiments in which a single dose of galactose was fed. Bell [31] reported 0.02% of hydrolyzed complex carbohydrate in the liver after galactose feeding to consist of material which was a nonfermentable reducing substance and thus presumably galactose.

Dodge [34] and Holt and Kajdi [35] reported the presence of dilated bladders in galactose-fed rats, but dilatation of the kidney pelvis has not been reported heretofore. The increased kidney-weight/body-weight ratio was a new observation. No particular element of the kidney appeared to be responsible for this hypertrophy. Again, the Best's-carmine-positive material was not stained by the iodine technique for glycogen, a fact indicating the formation of a "galactogen" in Henle's loops. No degenerative renal lesions were found in our animals.

Hernberg [14] reported testicular atrophy in alloxan-treated animals which was similar to that described here. He attributed the change to a protein deficiency, to which we also ascribe this change as well as the atrophic condition of the prostate and seminal vesicles.

The changes in the eye, especially those in the lens, are well documented [36] except for the fibroblastic proliferation of the anterior lens capsule. This has been noted as a complication of senile cataracts in humans.[37] The anterior synechiae and inflammation of the iris diaphragm have not been described hitherto by workers on galactose cataracts. Buschke [38] classified the experimental cataracts of the rat according to their slit-lamp appearances and etiologies. He stated that the cataracts induced by diabetes, galactose, and xylose result primarily from osmotic alteration in the serum due to the high serum carbohydrate levels and that these cataracts have a distinctive pattern of development quite different from the "dystrophic" cataracts resulting from amino-acid and riboflavin deficiencies. The corneal vascularization, iritis, and posterior synechiae found in the eyes of our galactose-fed animals indicate that perhaps the basic etiologies of these two types of experimentally induced cataracts are closely allied.

SUMMARY AND CONCLUSIONS

From the material presented it can be concluded that on a 70% carbohydrate diet containing an 18% casein component, galactose-fed rats are in a state of relative protein deficiency in comparison with their glucose-fed controls. This deficiency is due to increased urinary excretion of nitrogen-containing components. Among

33. Deuel, H. J., Jr.; MacKay, E. M.; Jewel, P. W.; Gulick, M., and Grunewald, C. F.: J. Biol. Chem. **101**:301, 1933.

34. Dodge, W. M., Jr.: Arch. Ophth. **14**:922, 1935.

35. Holt, L. E., Jr., and Kajdi, C. N.: Bull. Johns Hopkins Hosp. **74**:121, 1944.

36. Gifford, S. R., and Bellows, J.: Arch. Ophth. **21**:346, 1939.

37. Kirby, D. B., in The Eye and Its Diseases, edited by C. Berens, Ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 462.

38. Buschke, W.: Arch. Ophth. **30**:735, 1943.

the latter are peptides and amino acids. This increased urinary nitrogen excretion is believed to have its origin in part in increased metabolic demand on the available nitrogen for gluconeogenesis and in part in a competitive inhibition of amino acids and peptides by the renal tubules, which are saturated by galactose. Many of the pathologic observations can be correlated with a protein deficiency, including failure of growth, atrophy of the testicle, corneal vascularization, and the formation of lens cataracts.

The following conclusions can be drawn:

1. Young rats maintained on a 70% galactose diet with an adequate protein and salt intake have a positive calcium and phosphorous balance. They show no pathologic alterations in their bony structure.

2. Such animals excrete a high proportion of their ingested protein nitrogen. Peptides and amino acids are excreted in the urine in increased amounts in comparison with amounts excreted by the control glucose-fed rats.

3. Corneal vascularization, iritis, hydronephrosis, and testicular atrophy develop in rats maintained on such a galactose diet for a sufficient length of time. These observations suggest that the animals suffer from an amino-acid and protein deficiency.

4. Tryptophane supplied in amounts up to 2% of the diet is not protective against the cataract-forming properties of this diet.

MICROSCOPIC DIFFERENTIAL DIAGNOSIS OF LATENT CARCINOMA OF PROSTATE

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THERE HAS been instituted at the Francis Delafield Hospital a program which has as its aim the detection of carcinoma of the prostate while it is still confined to that organ and is in a potentially curable state. The procedure has included the wide surgical exposure of the posterior lobe of the prostate through a perineal incision, the removal of a transverse slice of the lobe, and its immediate examination by the quick frozen-section method. If a diagnosis of carcinoma could be made and the carcinoma was deemed operable, an immediate total perineal prostatectomy was done. At once it became apparent that good, well-stained sections must be prepared, but of supreme importance were reliable criteria for the recognition of latent microscopic carcinomas, which are the potentially curable ones. The purpose of this article is to relate our experiences with this method and report in detail the criteria we adopted for making a diagnosis of carcinoma as well as for differentiating it from the microscopic formations in the prostate with which it may be confused. The details of the clinical, sociological, and statistical aspects of this endeavor will be presented subsequently by Dr. Perry B. Hudson, of the Urological Service of the Francis Delafield Hospital, the initiator of the program.

Anyone who has been confronted with the problem can appreciate the difficulty in arriving at reliable criteria for the microscopic diagnosis of carcinoma of the prostate. Although there are a number of papers [1] concerning the microscopic

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1. (*a*) Bibus, B.: Das Prostatakarzinom, Wien. klin. Wchnschr. **53**:93-96, 1940. (*b*) Gaynor, E. P.: Zur Frage des Prostatakrebses, Arch. path. Anat. **301**:602-652, 1938. (*c*) Kahler, J. E.: Carcinoma of the Prostate Gland: A Pathologic Study, J. Urol. **41**:557-574, 1939. (*d*) Lewis, L.: Symposium on Diagnosis and Treatment of Premalignant Conditions: Precancerous Lesions of the Prostate, S. Clin. North America **30**:1777-1782, 1950. (*e*) von Meyenburg, H., and Cathomas, B.: Über die Häufigkeit des Prostata-Karzinoms in Zürich: Beitrag zur Frage der "okkulten" Karzinome, Schweiz. med. Wchnschr. **78**:473-475, 1948. (*f*) Moore, R. A.: The Morphology of Small Prostatic Carcinoma, J. Urol. **33**:224-234, 1935. (*g*)

(Footnote continued on next page)

diagnosis, they are not sufficiently specific or adequately illustrated to permit reliable application when a mistake may have serious consequences.

Included in this series were men with prostatic obstructive symptoms, but the majority were patients with minimal or no complaints who were found by rectal examination to have some significant abnormality of the gland. The latter group was the result of a survey conducted by the resident staff of the Francis Delafield Hospital in several of the municipal and private lodging houses in downtown New York City and will be referred to as the Bowery Series. The total group studied consisted of 131 patients for whom posterior lobe biopsies and studies of frozen sections were done, of whom 15 had obvious clinical carcinoma with metastases and were subjected to biopsy for confirmation purposes. Of the other 116, 100 were from the Bowery Series. In the group of 116 we found 24 considered to have unequivocal carcinoma and 4 additional whose lesion was considered equivocal. The series is, of course, not comparable to the several autopsy series [2] studied for the incidence of latent carcinoma, since there was some element of selection. It is of interest that in 13 of the 24 patients with carcinoma the condition was considered to be benign by the usual clinical standards and therefore represented true latent carcinoma.

In our procedure the gland was exposed via the perineum and a generous wedge of the posterior lobe was removed. This was split transversely through a plane paralleling the long axis, and half was frozen for a quick section after fixation in Bouin's solution; the other half was saved for permanent paraffin sections. The frozen sections were cut in the usual manner at approximately 7 to 10 μ and stained with Metachrome B. We found the procedure to be relatively simple once the technique of handling such a relatively large piece was perfected. Since our criteria were developed and changed during this series, it is not possible to evaluate correctly the accuracy of the frozen-section technique, but we feel that in itself it should offer no handicap to the diagnosis of carcinoma (Fig. 1). If the frozen-section diagnosis was benign, either no further surgery was done or definitive surgery for benign enlargement was performed. If the diagnosis was carcinoma and the condition operable, a radical perineal prostatectomy was done. In those instances in which the diagnosis was in doubt, further operative procedure was postponed pending the results of study of the paraffin sections.

In 16 of the cases of carcinoma, the entire gland was studied by step sections at approximately 2 to 5 mm. intervals. Whole-gland sections were used in two instances. No attempt was made to plot accurately the site or size of these tumors. Of the 24 carcinomas, 12 were apparently confined to the gland, 7 showed extension only into perineural lymphatics, and 5 had extended into the seminal vesicles.

Thus far we have seen four general histologic patterns of carcinoma, three of which were easily recognized. The cribriform arrangement (Fig. 2*A*), diffuse individual-cell infiltration (Fig. 2*B*), and what may be called medium-sized-gland

Oswald, W.: Häufigkeit und Genese des Prostatacarcinoms, Frankfurt. Ztschr. path. **55**:296-316, 1941. (*h*) Rich, A. R.: On the Frequency of Occurrence of Occult Carcinoma of the Prostate, J. Urol. **33**:215-223, 1935. (*i*) Walthard, B.: Die Häufigkeit und Histogenese des Prostatacarcinoms, Ztschr. urol. Chir. u. Gynäk. **43**:483-496, 1937.

2. Baron, E., and Angrist, A.: The Incidence of Occult Adenocarcinoma of the Prostate After 50 Years of Age, Arch. Path. **32**:787-793, 1941. Gaynor.[1b] Kahler.[1c] von Meyenburg and Cathomas.[1e] Moore.[1f] Oswald.[1g] Rich.[1h] Walthard.[1i]

carcinoma (Fig. 2C) were not difficult, since their patterns were distinctive, even though the cellular changes listed hereafter were frequently not found. The first two types, especially, were seen in more or less advanced cases. The pattern which occurred most frequently and was the most difficult may be called small-gland carcinoma (Figs. 3 and 4). This pattern may be related to the others, since it was seen sometimes in conjunction with them, but it often appeared alone. The chief

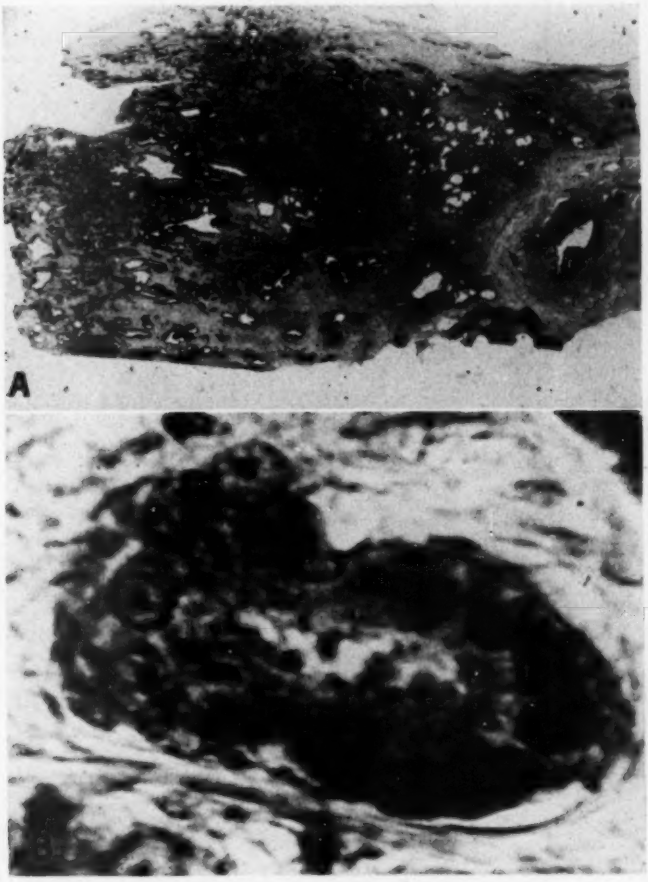

Fig. 1.—*A*, posterior lobe biopsy specimen from a case of extensive carcinoma; frozen section stained with Metachrome B; × 3.2. Small, closely packed glands have replaced a considerable part of specimen and extend into capsule (along upper margin). *B*, same case; a frozen section stained with Metachrome B; × 400, slightly enlarged. Cell details in one of the small glands are shown. Note prominent nucleoli.

difficulty in its recognition was differentiating it from other irregular small-gland patterns which we now feel are benign. There are three criteria which we believe are of definite value: 1. Glandular pattern. This is the most difficult to express and illustrate. It consists of a group of small irregular glands without any particular relation to the adjacent stroma or the normal glands. They appear to be growing

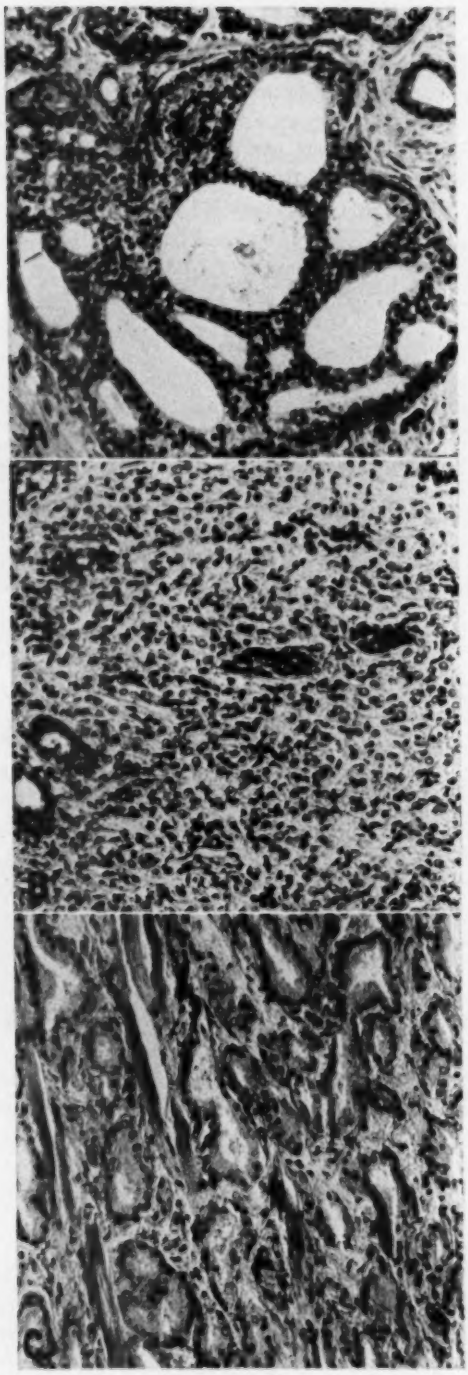

Fig. 2.—*A*, cribriform pattern in a case of carcinoma; × 100. *B*, a carcinoma with diffuse infiltration of individual cancer cells; × 100. *C*, medium-gland carcinoma; × 100. Glands are closely packed and stroma is sparse.

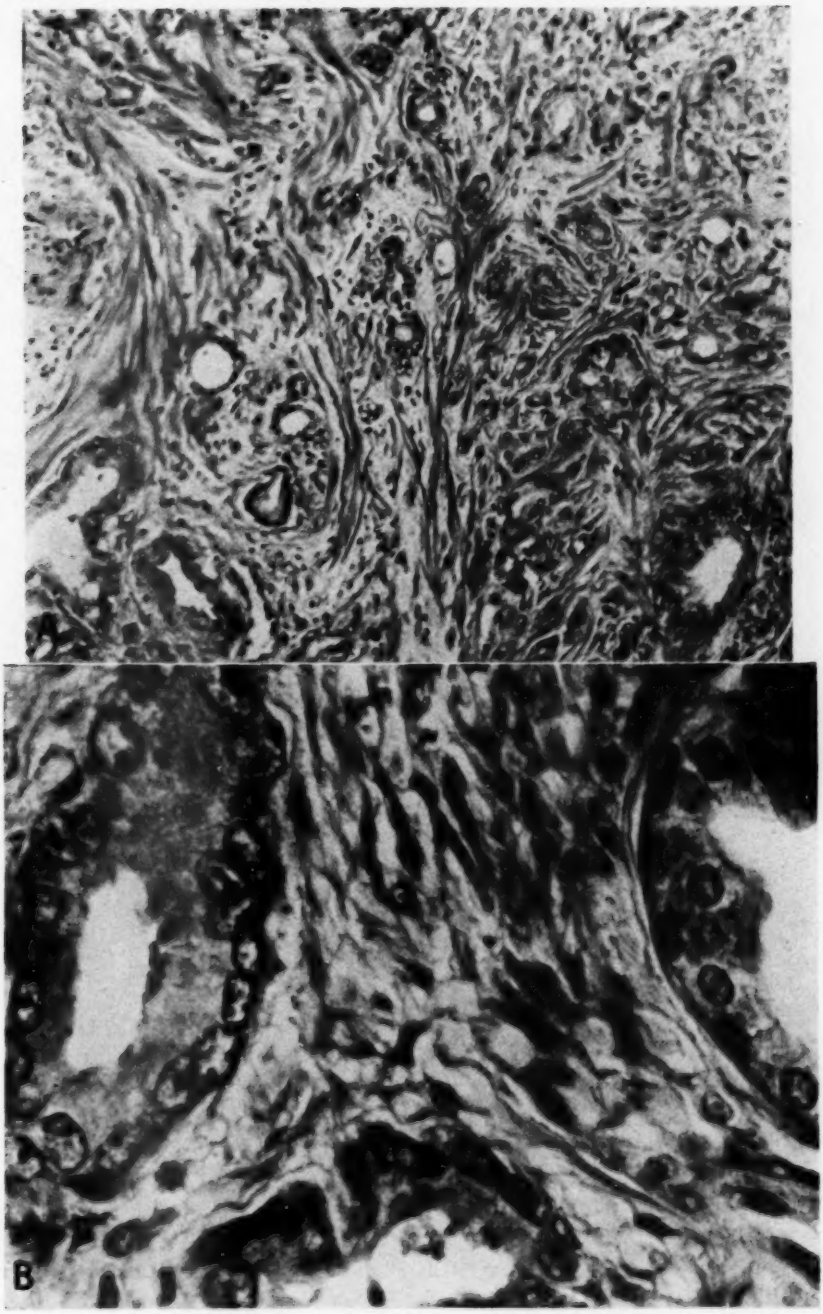

Fig. 3.—*A*, small-gland carcinoma; × 100. Small glands are arranged at random in loose stroma. *B*, same case; two small carcinoma glands and part of a larger gland (right) showing hyperplasia; × 480. Note prominent nuclei and peripherally arranged chromatin in small glands as contrasted with those in hyperplastic gland. The basal layer of cells is preserved in the latter.

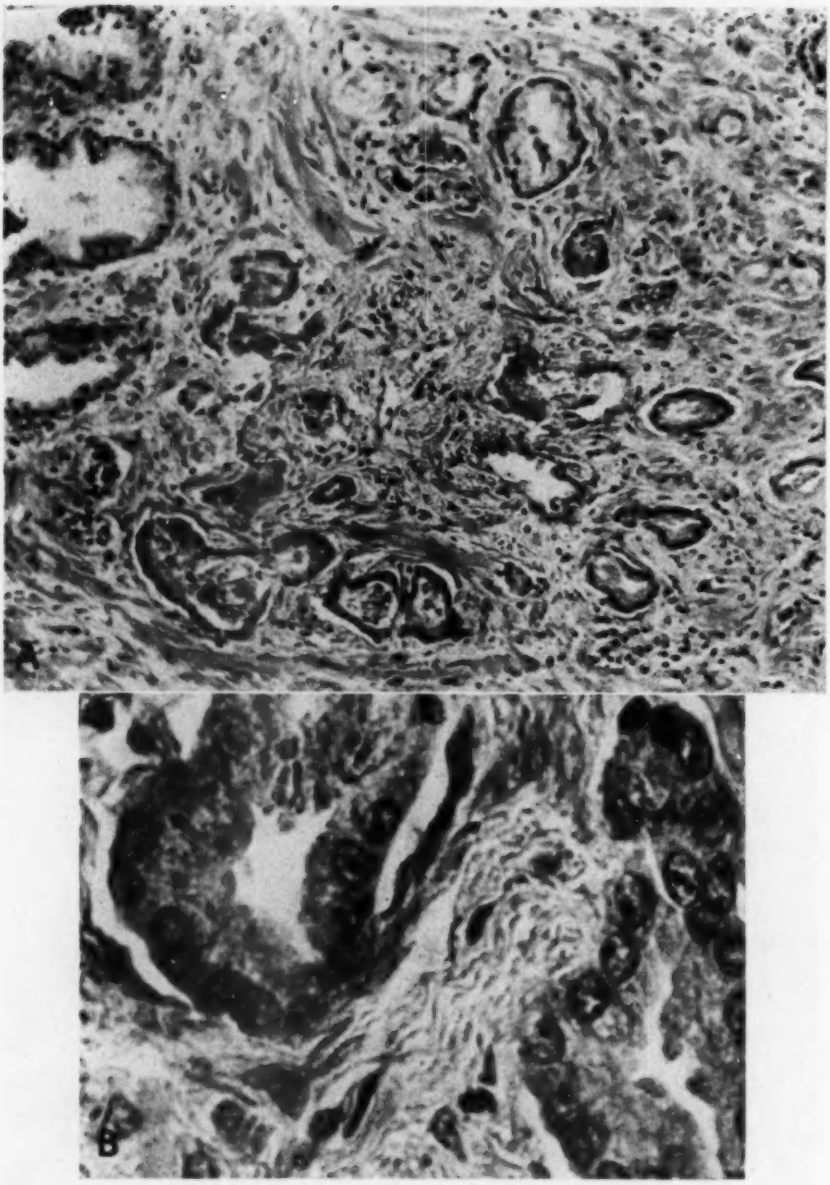

Fig. 4.—*A*, minimum small-gland carcinoma confined to this one low-power field. × 100. *B*, same case; × 480. Nucleoli are prominent and chromatin concentrated chiefly at periphery of nuclei; basal layer absent.

in a disorderly fashion without any evidence of distortion by atrophy, fibrosis, or compression. These observations are similar to those of other observers.[3] 2. The arrangement of the epithelium within the glands. In most of the larger acini of the non-neoplastic prostate and some of the smaller ones, there is a distinct basal layer of epithelium (Fig. 5). The cells usually have small, elongated, uniformly

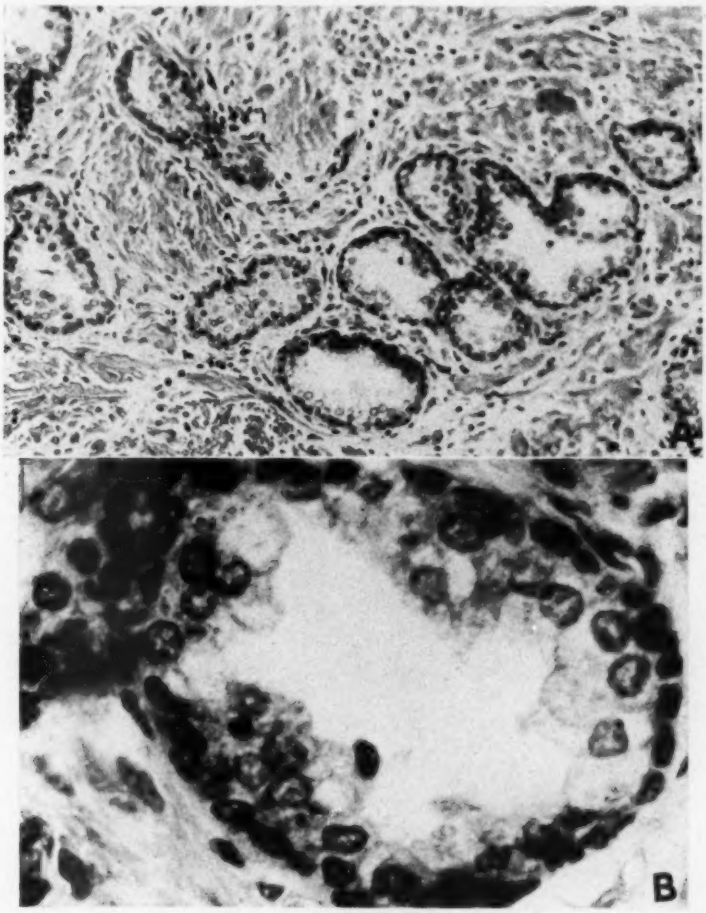

Fig. 5.—*A*, prostatic acini showing a slight degree of hyperplasia; × 100. The layer of flattened basal cells is well preserved. *B*, same case; × 400. Cells of basal layer have rounded or elongated nuclei.

hyperchromatic nuclei arranged at right angles to the acinar lining cells. This basal layer is not always present in benign small glands, so that its absence is not an absolute criterion of carcinoma. Conversely, however, we have not seen it in any case in which the diagnosis was cancer. This point was briefly mentioned by

3. Bibus.[1a] Gaynor.[1b] Moore.[1f] Oswald.[1g] Walthard.[11]

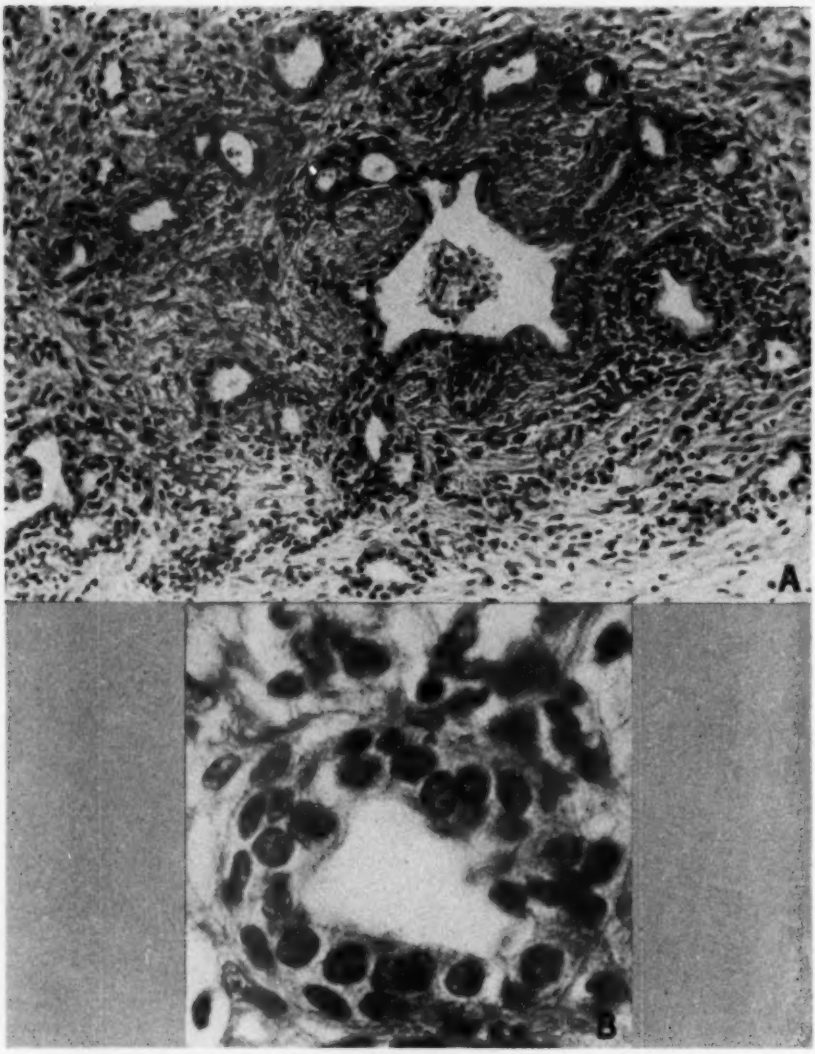

Fig. 6.—*A*, lobular hyperplasia; × 90. A large branching duct-like space is surrounded by clusters of small acini. *B*, same case; × 400. Nuclear chromatin is evenly distributed. The basal layer of cells as seen here is not always preserved.

Lewis but not illustrated. 3. Cellular details. The characteristics of malignant cells in general are notoriously absent in many types of prostate carcinoma. We have found, however, that in this small-gland carcinoma there are certain nuclear changes which thus far have always been present. The most prominent of these is the presence of relatively large, deeply staining nucleoli. These nucleoli are sometimes multiple but rarely are more than two per nucleus. Small nucleoli are frequently seen in "normal" or hyperplastic epithelium, but seldom do they attain this size except in carcinoma of the small-gland type. In addition, the nuclear chromatin is usually sparse or absent in the central portion of the cell, being concentrated at the nuclear membrane. This observation is in contrast to the usual vesicular nuclei in benign glands (Figs. 3*B* and 4).

All of our material has been fixed in Bouin's solution as soon as possible after removal, which may perhaps influence beneficially the staining of nuclear details. In several instances of similar findings in Zenker-fixed autopsy specimens removed at varying intervals after death, these nuclear changes have not been so prominent.

Invasion of the capsule, perineural spaces, lymphatic vessels, or seminal vesicles we have considered to be definite indications of malignancy. In every instance of small-gland carcinoma in which such invasion occurred, the cellular and nuclear changes listed were prominent. In this respect these criteria are thought to be significant. However, since the series is relatively small and follow-up examinations were incomplete, their ultimate validity cannot be estimated.

The basement membrane, at least as seen in hematoxylin and eosin or silver preparations, was of little help. It was frequently absent about small benign glands and not infrequently present surrounding carcinomatous glands, even in their metastases. Mitoses were rarely seen in the prostate gland and occurred with about equal frequency in benign and in malignant conditions.

Of the types of benign small-gland aberrations seen, by far the most frequent and most confusing was what may be called lobular hyperplasia. This consisted of a focal or diffuse collection of duct-like spaces, usually in the posterior lobe or periphery of the lateral lobes. The ductules were frequently stellate, and each of the branches was surrounded by a cluster of small acini, somewhat reminiscent of the structure of nonlactating female mammary glands (Fig. 6). Where the pattern was well preserved it was easily recognized and usually was not confused with carcinoma. However, these areas often underwent fibrosis, atrophy and/or compression, so they could mimic the appearance of an infiltrating carcinoma (Fig. 7). The characteristics of the individual cells, with their small rounded or oval nuclei, evenly distributed chromatin, and scant cytoplasm, did not usually change. We did not, in this material, see any definite evidence that the glands of this pattern could behave like a malignant tumor; i. e., invade the capsule, perineural spaces, or seminal vesicle. In at least four instances a moderate amount of lobular hyperplasia was seen along with a carcinoma, but in none was it possible to demonstrate a continuity. We cannot deny that carcinoma may develop from lobular hyperplasia, since our material was somewhat limited. The pattern in various stages of preservation was seen often enough for us to feel that it probably represented a form of proliferation of prostatic epithelium and not neoplasia. Other types of small glands were occasionally seen—atrophic, compressed, dilated, or distorted by neigh-

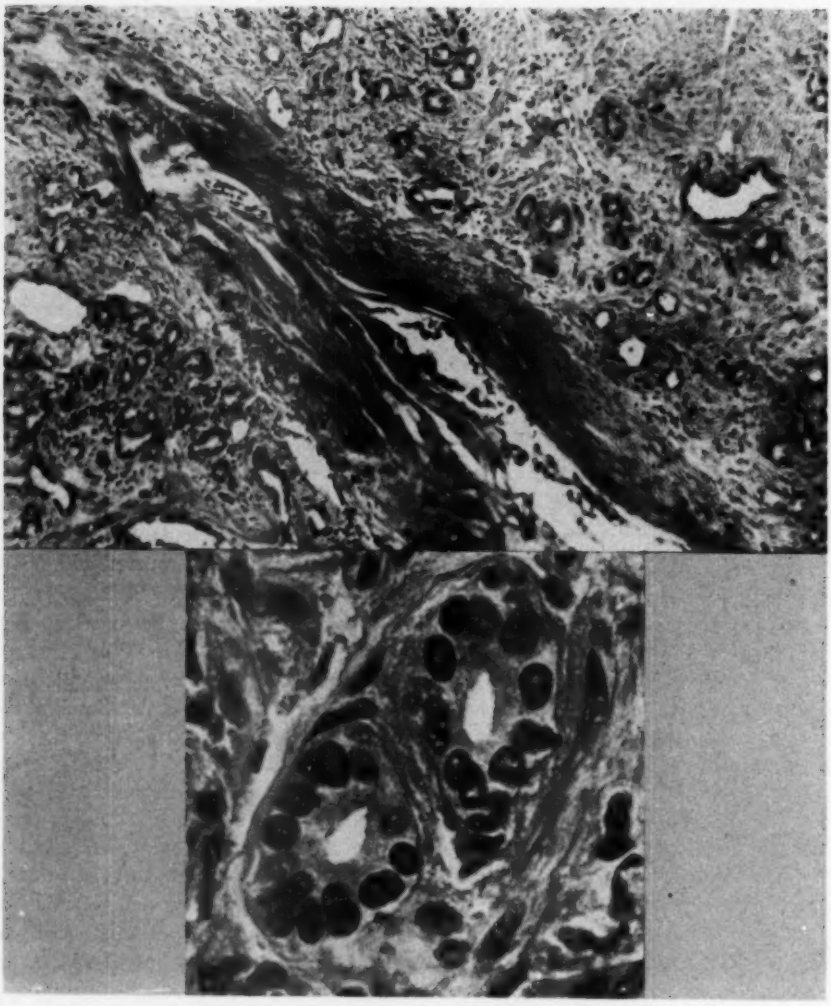

Fig. 7.—*A*, distorted lobular pattern; × 100. Note large wedge of dense collagenous tissue. *B*, same case; small glands with rounded, fairly uniform nuclei; × 400. Nuclear chromatin is evenly distributed. An occasional basal cell remains.

boring inflammation, fibrosis, calculi, or corpora amylacea. Despite their irregular appearance under low power magnification, the cells in these glands lacked the characteristics enumerated.

The survey of patients from the Bowery is still in progress, and these criteria are being used. It is hoped that after a sufficient number have been studied, and especially after the follow-up examinations are completed, more information will be available concerning carcinoma of the prostate.

SUMMARY

The results of the quick frozen-section method as used routinely in perineal prostatic surgery have been briefly presented. We feel that this method is a useful cancer-finding technique.

Several criteria, chiefly cellular, have been presented which in the light of present knowledge are useful in the diagnosis of carcinoma of the prostate.

Some patterns of irregular small glands have been shown which superficially resemble carcinoma but which we feel are benign.

MALE PSEUDOHERMAPHRODITISM IN THREE SIBLINGS

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AND
F. ZANARDI, M.D.
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IN A RECENT paper, Wachstein and Scorza (1951) [1] called attention to a particular type of male pseudohermaphroditism characterized by female habitus, absence of uterus, short vagina, absence of axillary and pubic hair, and presence of male gonads. These authors reported that their patient had never menstruated and had normal external genitalia of the female type. Hormonal assays indicated gonadal insufficiency with low production of estrogens and increased urinary output of gonadotropic hormone. A marked hereditary factor was suggested.

Wachstein and Scorza, on reviewing the literature, collected 20 cases of this syndrome; to these we can add two more, one described by Wilkins (1950)[2] and the other by Cook [3] (1950). Cook has described two cases of hernial "sac" testes found in "female" children. More recently Nelson (1951) [4] has published five new cases, three of them concerning married persons.

We are now able to make a further contribution to this interesting subject; in our patients the hereditary factor is quite evident, since three female members of the same family showed evidence of the syndrome. Hormonal assays were also performed.

REPORT OF CASES

P. F., a 23-year-old woman, the first-borne of five sisters, had never menstruated. She had been operated on in Switzerland (Sanatorium des Alpes Valdoises of Leydin) three years previous to our examination, for a painful swelling in each inguinal ring. This was considered to be an ovarian hernia, and at operation the inguinal swellings were found to be apparently of gonadal origin. These were reposited within the peritoneal cavity.

When the patient was reexamined by us she presented pronounced female sex characteristics; she had well-developed breasts and a regular growth of pubic and axillary hair. She stated that she had normal sexual relationships. She had normal external genitalia, a clitoris of normal size, and a vagina 8 cm. long ending blindly. At gynecological examination no uterus was palpable.

P. P., aged 20 years, sister of the former patient, showed bilateral painful swellings in the inguinal regions. She stated that these had appeared two years previous to our examination.

From the Department of Pathological Anatomy, University of Milan.

1. Wachstein, M., and Scorza, A.: Am. J. Clin. Path. **21**:10, 1951.

2. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., Charles C. Thomas, Publisher, 1950, p. 271.

3. Cook, J.: Brit. J. Urol. **22**:211, 1950.

4. Nelson, W. O.: Abstracted in Federation Proc. **10**:97, 1951.

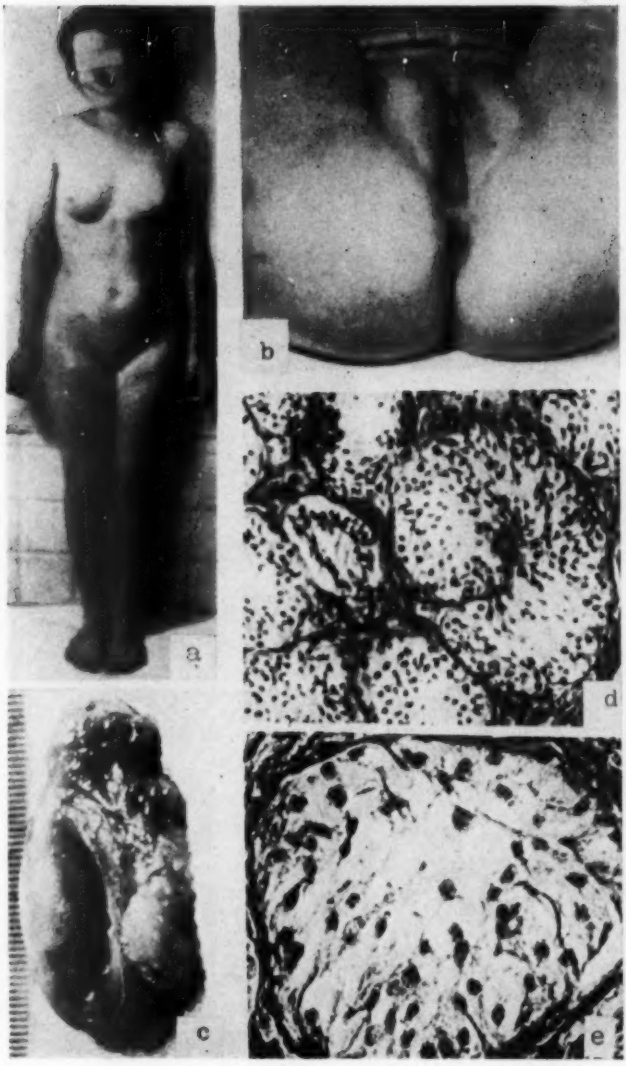

Fig. 1 (P. P., 20 years old).—(*a*) Normal female habitus. (*b*) Absence of pubic hair and hypotrophic external genitalia; note the swellings near the vulva. (*c*) Right testis removed by operation. (*d*) and (*e*) Testicular tubules lined by Sertoli cells.

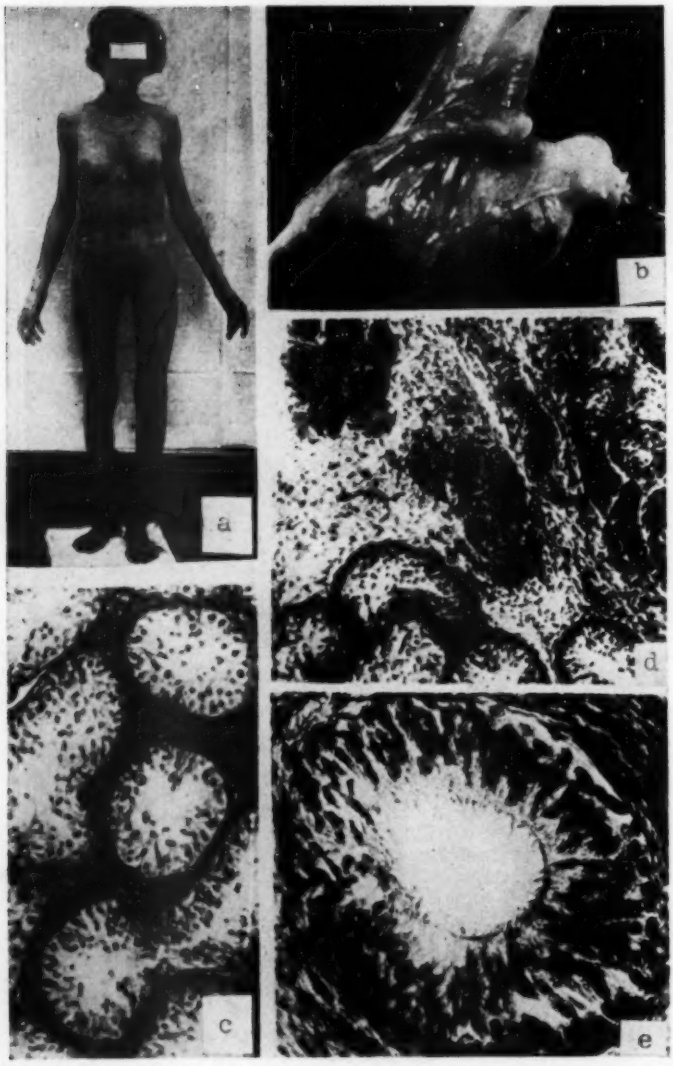

Fig. 2 (P. J., 16 years old).—(*a*) Slight cubitus valgus. (*b*) Testis with epididymis and spermatic cord. (*c*) Testicular tubules. (*d*) Leydig cells in clumps in the connective tissue of the stroma. (*e*) Epididymal tubule.

Menstruation had never occurred. Her psychological behavior was normal, without homosexual tendencies. She had had sexual relationships, but on questioning, she stated that she did not feel any particular attraction to the male sex.

The patient was a woman with a feminine habitus, a smooth skin, a feminine voice, and well-developed breasts. However, there was absence of pubic and axillary hair, with only scanty growth of hair around the vulva (Figs. 1*A* and *B*). The labia majora and minora were somewhat small; the clitoris was normal in size but not erectile, and the vagina was 4 cm. long with a blind ending. No uterus was palpable. In each inguinal region there were two oval-shaped tender swellings, each the size of a hazelnut; the swelling on the right side could be reposited into the abdominal cavity by pressure.

An exploratory operation revealed the absence of uterus, Fallopian tubes, and ovaries. The structures situated at the inguinal rings were removed in two parts. They resembled testes with epididymis and vaginalis propria and with a spermatic cord entering the inguinal ring. No vas deferens was present; small cysts at the poles of the testes were observed (Fig. 1*C*). The structures removed weighed 7.5 and 8 gm. respectively. For two years following the operation the patient did not complain of any menopausal symptoms.

P. J., the third sister belonging to the same family, was 16 years of age. She had not yet menstruated and showed feminine habitus but absence of pubic and axillary hair, well-developed breasts, hypotrophic labia, and a normal clitoris (Fig. 2*A*). A slight cubitus valgus was noticeable, but there was neither shortness of the neck nor dwarfism. Two reducible swellings were palpable at the inguinal rings. Absence of uterus, Fallopian tubes, and ovaries was verified by operation.

Hormonal Assays Indicating Gonadol Insufficiency

Case	Clinical Condition	17-Keto-steroids, Mg./Day	Gonado-tropins, R. U./Day	Estrogens, Mg./Day
P. F.	Intact	34.12	51	82.1
P. P.	Intact	13.4	12	130.1
	5 days after semicastration	16.00	96	40.0
	1 month after castration	14.85	53	44.5
	1 year after castration	31.70	40	72.0
P. J.	Intact	11.20	..	....
	After semicastration	5.80	28	62.0

The structure present in the right inguinal region was removed. Macroscopic examination suggested a testis with epididymis (16 gm.); a spermatic cord was also present but no vas deferens (Fig. 2*B*). Several small cystic structures were attached to each pole of the testis.

The two other sisters of the family, aged 22 and 19 years respectively, had menstruated normally. Somatic and psychological examination showed no abnormalities. The mother of the five sisters had repeatedly suffered from rheumatic fever, and at present is affected by a chronic pancarditis.

Hormonal Assays.—Determinations of the urinary excretion of estrogens, 17-ketosteroids, and gonadotropins were performed repeatedly on the three sisters.

Estrogens were assayed by the method of Kober (normal values 60 to 120 mg. daily), 17-ketosteroids by the method of Talbot (normal range 8 to 15 mg. per day in the female), and pituitary gonadotropins were assayed in immature female rats, with increase of the uterine weight as the indicator (normal range 5 to 8 rat units daily).

MICROSCOPIC EXAMINATION

The two testes removed from P. P. and the right testis removed from P. J. were similar in microscopic appearance (Figs. 1*D* and *E*, and 2*C*, *D*, and *E*). They were composed of tubules surrounded by scanty connective tissue which contained many Leydig cells in clumps or singly. The tubules were lined by Sertoli cells in more or less advanced differentiation. There was no sign of spermatogenesis.

Lipid material was demonstrable in most of the interstitial cells as well as in testicular tubules. Epididymal and rete testis structures were also observed. No adenomatous growth was present.

SUMMARY

Three cases of an uncommon type of pseudohermaphroditism, occurring in three members of the same family, are reported. Each of these patients showed normal female habitus and breast development, absence or scantiness of pubic hair, smallness of external genitalia. The vagina was short, and no enlargement of the clitoris was found. In two cases the absence of ovaries was ascertained by surgical exploration. Swellings in the inguinal region were found to be due to testicular structures, without evidence of spermatogenesis. The tubules were lined with more or less differentiated Sertoli epithelium and surrounded by a large number of Leydig cells.

Hormonal assays showed a normal or slightly increased urinary output of 17-ketosteroids and a normal or subnormal excretion of estrogens. Estrogens decreased markedly following partial or total castration.

Urinary gonadotropins were high and increased after castration. The decrease of the urinary estrogens after operation suggests a regular secretion of these hormones by the Sertoli and/or the Leydig cells. The increase of the gonadotropins under the same conditions suggests that this secretion may inhibit the gonadotropic activity of the anterior lobe of the pituitary.

HISTOCHEMICAL CHANGES IN IRRADIATED OVARIES

I. Succinic Dehydrogenase Activity

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SAM W. DENHAM, M.D.
AND
M. HARLAN JOHNSTON, M.D.
ATLANTA

FOLLOWING irradiation, certain changes in tissue probably precede lesions demonstrable by conventional histologic methods. Among the vital processes first presenting themselves for investigation in pursuance of this concept are those of the enzyme systems. Various of these systems are said to be sensitive to irradiation.[1]

A new method for studying enzymatic activity in tissues is the demonstration of succinic dehydrogenase by means of certain tetrazolium salts.[2] These compounds as indicators of dehydrogenase activity in tissue are fairly recent additions to the histochemical armamentarium.[3] Neotetrazolium (*p, p'*-diphenylene bis 2-[3,5 diphenyl tetrazolium chloride]) is pale yellow in solution and is converted to an insoluble purple-to-black compound of the formazan group at the site of active metabolic processes.[4] If an excess of sodium succinate is added as a substrate, it is reasonable to suppose that much of the reduction is due to succinic dehydrogenase.[2] Previously we found[5] that in the ovaries of rabbits undergoing Friedman tests, maximum formazan deposition correlated well with areas of maximum growth and presumed cell metabolism.

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This investigation was supported by a research grant (C-1486) from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

1. Dale, W. M.: The Effect of X-Rays on Certain Enzymes, Biochem. J. **34**:1387, 1940. Barron, E. S. G.; Dickman, S.; Muntz, T. A., and Singer, T. P.: Studies on the Mechanism of Action of Ionizing Radiations: I. Inhibition of Enzymes by X-Rays, J. Gen. Physiol. **32**:537, 1949.

2. (*a*) Seligman, A. M., and Rutenburg, A. M.: Histochemical Demonstration of Succinic Dehydrogenase, Science **113**:317, 1951. (*b*) Shelton, E., and Schneider, W. C.: On the Usefulness of Tetrazolium Salts as Indicators of Dehydrogenase Activity, Anat. Rec. **112**:61, 1952.

3. Zweifach, B. W.; Black, M. M., and Shorr, E.: Histochemical Alterations Revealed by Tetrazolium Chloride in Hypertensive Kidneys in Relation to Renal VEM Mechanisms, Proc. Soc. Exper. Biol. & Med. **74**:848, 1950.

4. Antopol, W.; Glaubach, S., and Goldman, L.: The Use of Neotetrazolium as a Tool in the Study of Active Cell Processes, Tr. New York Acad. Sc. **12**:156, 1950.

5. Foraker, A. G., and Denham, S. W.: Neotetrazolium in Determination of Succinic Dehydrogenase Activity in the Ovary, Proc. Soc. Exper. Biol. & Med. **80**:132, 1952.

Plant seeds irradiated with x-rays and then treated with tetrazolium salts show that the irradiation effect can be detected by changes in the reducing power of the enzyme systems and can be measured by the amount of colored formazan produced.[6] It seemed of interest to investigate the effects of x-rays as seen in an organ which appears to have succinic dehydrogenase in abundance [7] and is well known as sensitive to irradiation.[8]

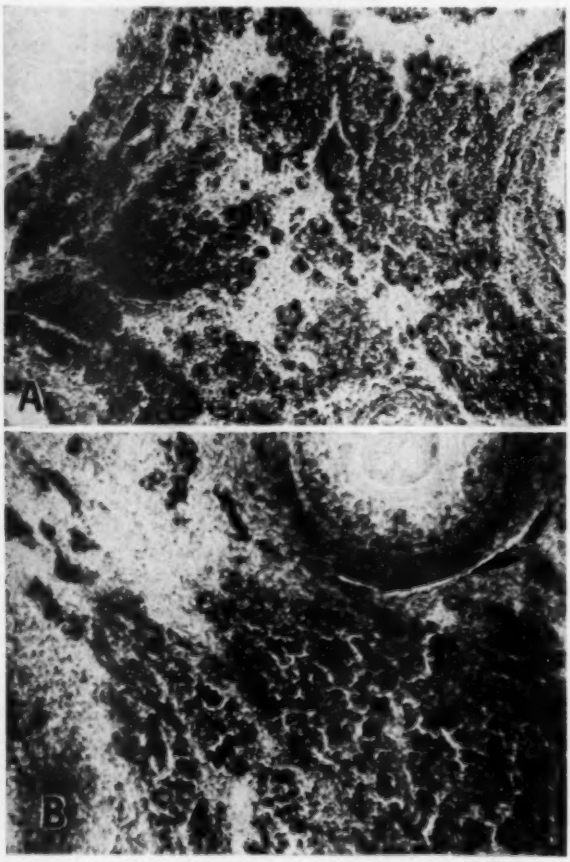

Fig. 1.—Neotetrazolium sections of ovaries from a rabbit injected with urine from a nonpregnant woman. *A*, area of the right (nonirradiated) ovary showing cystic follicles, ova, and stromal cells outlined by formazan deposition; × 75. *B*, detail of the same ovary showing ovum with formazan deposition in stromal cells and in follicle cells of the ovum; × 165.

6. Gierlach, Z. S., and Krebs, A. T.: The Tetrazoles as Indicators of Radiation Damage, Project No. 6-64-12-06, Medical Department Field Research Laboratory, Fort Knox, Kentucky, 1950.

7. Meyer, R. K., and McShan, W. H., cited by Engle, E. T.: Menstruation and Its Disorders, Springfield, Ill., Charles C Thomas, Publisher, 1950, p. 79. Foraker and Denham.[6]

8. Warren, S.: Effects of Radiation on Normal Tissues: VIII. Effects on the Gonads, Arch. Path. **35**:121, 1943.

In the present study, four weeks after administration of a tissue dose of 400 r to the left ovary, the irradiated ovaries of rabbits revealed marked diminution in number of ova, change in appearance in surviving ova, and lessening of response to hormonal stimulation, as in the Friedman test. There was little reaction of the stromal cells, as indicated by their formazan uptake (succinic dehydrogenase activity).

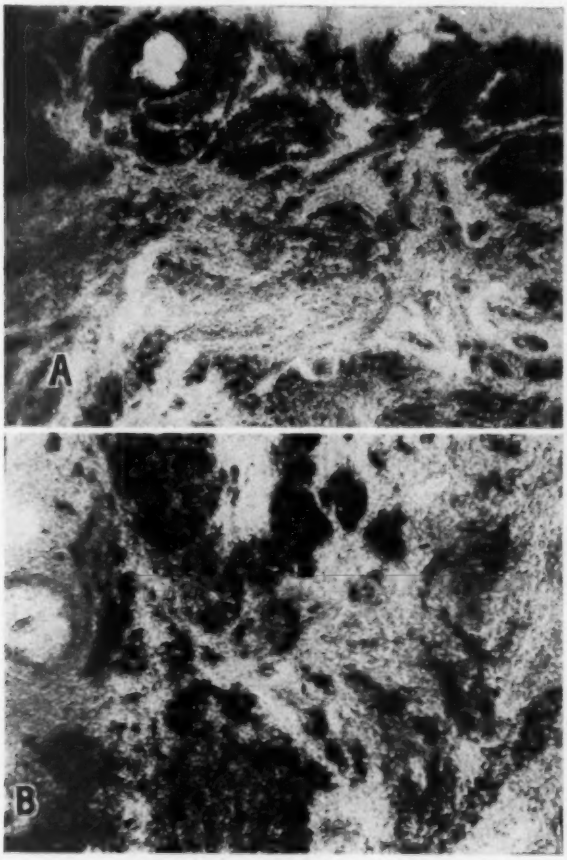

Fig. 2.—*A*, area of the left (irradiated) ovary of the rabbit whose right (nonirradiated) ovary is illustrated in Figure 1, showing the zone of failure of neotetrazolium reaction (top) seen in all blocks. No cystic follicles are present. Only stromal cells show formazan deposition; × 75. *B*, detail of the same ovary showing deposition in stromal cells and scarred shrunken ovum at the left; × 165.

MATERIALS AND METHODS

Twelve virgin female rabbits ranging from 6 to 8 weeks in age and from 1,180 to 3,140 gm. in weight were each given 400 r in air in a single dose to a 6.0-cm. external port over the left ovary. The factors of irradiation were: constant potential 200 kv. at 18 ma. with a half-value layer of 1.2 mm. Cu. The distance was 50 cm. with a dosage rate of 50 r per minute. With these factors at a depth of 2.0 cm., the tissue dose to the ovary is approximately the same as the air dose.

Four weeks later six of the rabbits were given intravenous injections of urine from nonpregnant women, and six, of urine from pregnant women, according to a standard routine for the Friedman test, except that the second injection was given after a 24-hour interval.[9] Forty-eight hours after the first injection, the nonirradiated ovaries of all rabbits presented the classic appearance of either the negative (nonpregnant) or the positive (pregnant) Friedman test.[10] In contrast, the irradiated ovaries were smaller, paler, and firmer.

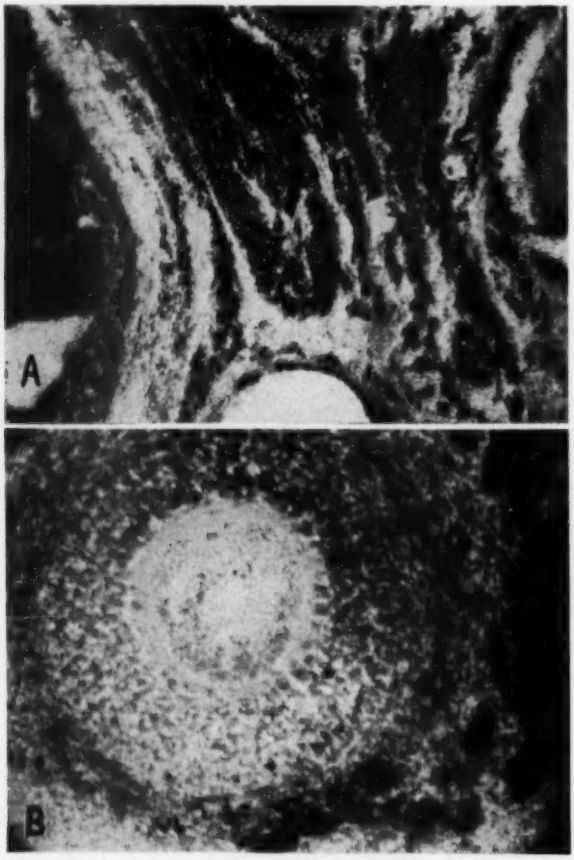

Fig. 3.—Neotetrazolium sections of ovaries from a rabbit injected with urine from a pregnant woman. *A*, area of the right (nonirradiated) showing walls of corpora hemorrhagica with formazan deposition in cells of these walls and in stromal cells; × 75. *B*, detail of the same ovary showing an ovum, with clear-cut formazan deposition in stromal cells and in follicle cells and little formazan deposition in the ovum, including the zona pellucida; × 330.

Fresh blocks from each ovary (about 3 mm. in thickness) were separately placed in flasks containing 4.5 ml. of 1% neotetrazolium in 0.1 M phosphate in isotonic sodium chloride buffered

9. Wolf, W.: Endocrinology in Modern Practice, Philadelphia, W. B. Saunders Company, 1936, p. 957.

10. Friedman, M. H., and Lapham, M. E.: A Simple, Rapid Procedure for the Laboratory Diagnosis of Early Pregnancies, Am. J. Obst. & Gynec. **21**:405, 1931.

to pH 7.4. To each flask, 0.5 ml. of 0.3 M sodium succinate was added.[5] Incubation with gentle agitation at 37 C. for one hour followed. The blocks were then fixed in neutralized 10% formalin. Frozen sections (15 μ) from these blocks were mounted in acacia.

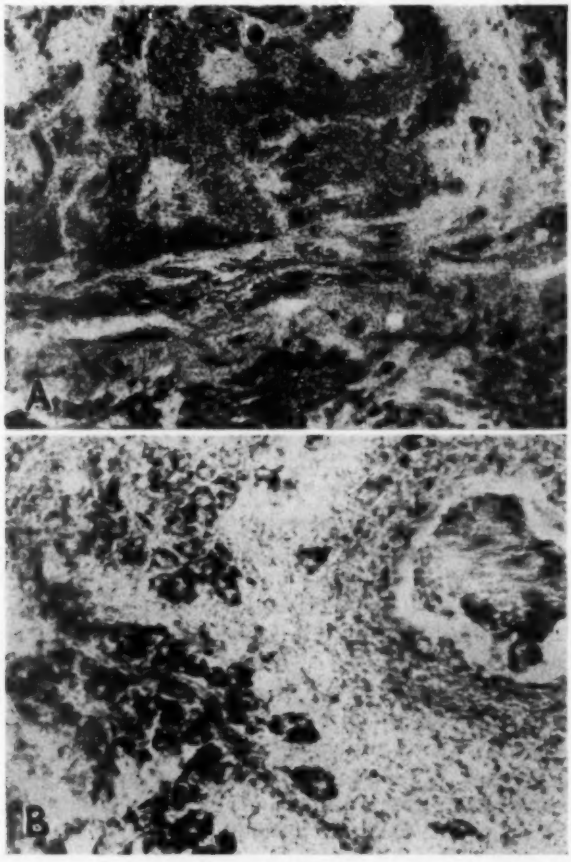

Fig. 4.—*A*, area of the left (irradiated) ovary of the rabbit whose right (nonirradiated) ovary is illustrated in Figure 2, showing formazan deposition only in stromal cells and about vessels. Several light, rounded areas represent sites of scarring of ova; × 75. *B*, detail of the same ovary showing a scarred shrunken ovum at the right, with little formazan deposition in or adjacent to it. Stromal cells at the left show distinct formazan deposition. Clear areas in the centers of the cells represent locations of nuclei; × 330.

RESULTS

In all blocks there was a peripheral zone of failure of the reaction.[2b] In the right ovaries no effect of radiation was seen. These ovaries from rabbits injected with urine from nonpregnant women contained numerous ova, with formazan deposition in the follicle cells of the ova, in the granulosa cells of the numerous cystic follicles, and in the stromal cells (Fig. 1).[5] At the hilum of the ovary, formazan deposition could be seen about the vessels. The nonirradiated ovaries of rabbits injected with

urine from pregnant women also contained numerous ova, with formazan deposition in the follicle cells of the ova. Formazan deposition was much heavier in the cell layers of the corpora lutea and corpora haemorrhagica (Fig. 3).[5] Formazan-containing stromal cells were present in these ovaries but were much less prominent than in the nonirradiated Friedman-negative ovaries.

In the irradiated ovaries, very few ova were found. Those that survived tended to have a pale shrunken refractile appearance with little or no zona pellucida and few or no adjacent formazan-containing follicle cells (Figs. 2 and 4). In the ovaries from rabbits injected with urine from nonpregnant women, little attempt at cystic follicle formation was found. In the ovaries from rabbits injected with urine from pregnant women, an occasional abortive attempt at formation of a hemorrhagic cystic follicle was seen, but no florid corpora lutea or corpora haemorrhagica were demonstrated.

The irradiated ovaries from rabbits injected with urine from pregnant women and those injected with urine from nonpregnant women were similar in their basic characteristics. In all, formazan-containing stromal cells seemed especially abundant. These were probably concentrated, owing to the lack of other elements of the normal ovaries. However, there was no reason to feel that the stromal cells of the irradiated ovaries showed any diminution in their number or in their succinic dehydrogenase activity, as manifested by formazan deposition.

COMMENT

In certain respects this study has reiterated the known phenomenon that the ova are more sensitive to radiation than are stromal cells.[5] Since the ova and adjacent follicle cells were so markedly damaged, it is not surprising that the ability of the ovaries to respond to hormonal stimulation was seriously compromised. The attempts of some irradiated ovaries of rabbits injected with urine from pregnant women to form hemorrhagic follicles may reflect the more potent hormonal content of this urine as regards stimulation of ovarian cellular proliferation.[11] The survival and apparent high degree of enzyme content of stromal cells is consistent with known effects of moderate irradiation on the ovary.[8]

In planning this study, consideration was given to extraction of reduced neotetrazolium from the ovaries with an organic solvent and subsequent photometric determination of the amount of reduced neotetrazolium per unit weight of ovary.[12] Our results do not suggest that such a procedure would have been of material assistance in determining radiation effect in this context. The structures damaged formed only a small part of the entire ovaries. If the content of hemorrhagic follicles had been included in ovary weight during this postulated computation, the results might have been confusing indeed. The location of the reaction within specific cells has thus provided information probably not available from more general chemical methods.[13]

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11. Friedman and Lapham.[10] Foraker and Denham.[5]

12. Black, M. M.; Kleiner, I. S., and Speer, F. D.: Effects of Enzyme Inhibitors on In Vitro Dehydrogenase Activity of Cancer Tissue Slices, Proc. Soc. Exper. Biol. & Med. **77**:611, 1951. Gierlach and Krebs.[6]

13. Fitzgerald, P. J., and Engstrom, A.: The Use of Ultraviolet Microscopy, Roentgen-Ray-Absorption, and Radioautographic Techniques in the Study of Neoplastic Disease, Cancer **6**:643, 1952.

Although the stromal cells showed little effect of irradiation after this four-week interval, we cannot say that their succinic dehydrogenase activity might not have been seriously diminished within a shorter period after irradiation or with a higher radiation dose.

SUMMARY

The left ovaries of 12 rabbits were subjected to external 200 kvp irradiation for a single dose of 400 r. Four weeks later six of the rabbits were used in negative and six in positive Friedman tests. Tissue from all ovaries was incubated in neotetrazolium with succinate to demonstrate succinic dehydrogenase activity. The results showed:

1. Little evidence of irradiation damage to stromal cells, either in general pattern or in succinic dehydrogenase activity, as manifested by formazan deposition in irradiated and nonirradiated ovaries.

2. Obliteration of most of the ova in irradiated ovaries. Those remaining were largely atretic, with little follicle-cell formation.

3. Little evidence of ability of the irradiated ovaries to respond to the hormonal stimulation of the Friedman test.

BILATERAL DUCTUS ARTERIOSUS REPRESENTING PERSISTENCE OF EACH SIXTH AORTIC ARCH

Report of a Case in Which There Were Associated Isolated Dextrocardia and Ventricular Septal Defects

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IN DEVELOPMENT of the aortic arch system, it is known from embryologic studies that at one stage the system includes a sixth (pulmonary) aortic arch on each side. The right and left pulmonary arteries arise as branches of these arches. The right sixth arch disappears beyond the point of origin of the right pulmonary artery. In an 11-mm. human embryo Congdon [1] found evidence that this segment was beginning to disappear. In an 18-mm. embryo it had disappeared; only the proximal part of the right sixth arch, that from which the right pulmonary artery arose, remained. On the left side the corresponding portion of the sixth arch persists as the ductus arteriosus.

Certain malformations are characterized by abnormal retention or disappearance of the elements of the sixth (pulmonary) aortic arches. For example, disappearance of the left sixth arch beyond the origin of the left pulmonary artery and persistence of the entire right sixth arch result in the presence of a ductus arteriosus on the right and none on the left. Loss from each sixth aortic arch of the portion beyond the origin of the respective pulmonary artery yields an aortic arch system in which there is no ductus arteriosus.

Rarest of all malformations involving abnormal retention or disappearance of one or the other of the two sixth aortic arches are those in which these arches persist in their entirety. In this article we are placing on record such a case. From the standpoint of gross anatomy the case may be designated as one of bilateral ductus arteriosus. The rarity of this anatomic arrangement is sufficient reason for placing a description of the specimen on record. Perhaps of greater significance, however, is that realization of its possible occurrence is helpful to one who attempts to relate the various anatomic types of malformations of the aortic arch system. In the specimen to be described there were associated serious malformations of the heart, but the primary purpose of this paper is to emphasize the occurrence of a ductus arteriosus on each side.

From the Sanitarium Clinic (Dr. Kelsey and Dr. Gilmore) and the Section of Pathologic Anatomy, Mayo Clinic (Dr. Edwards).

1. Congdon, E. D.: Transformation of the Aortic-Arch System During the Development of the Human Embryo, Contrib. Embryol. **14**:47, 1922.

REPORT OF CASE

The patient was a boy 10 months of age. Nothing abnormal was noted concerning either the gestation or the delivery. In the early neonatal period the infant seemed entirely normal. Cyanosis was first noted at 5 weeks of age. From this time until death at 10 months, there was gradual progress in intensity of the cyanosis, although periods when the patient was relatively free from cyanosis and the accompanying dyspnea intervened. The child died in a period of intensified cyanosis.

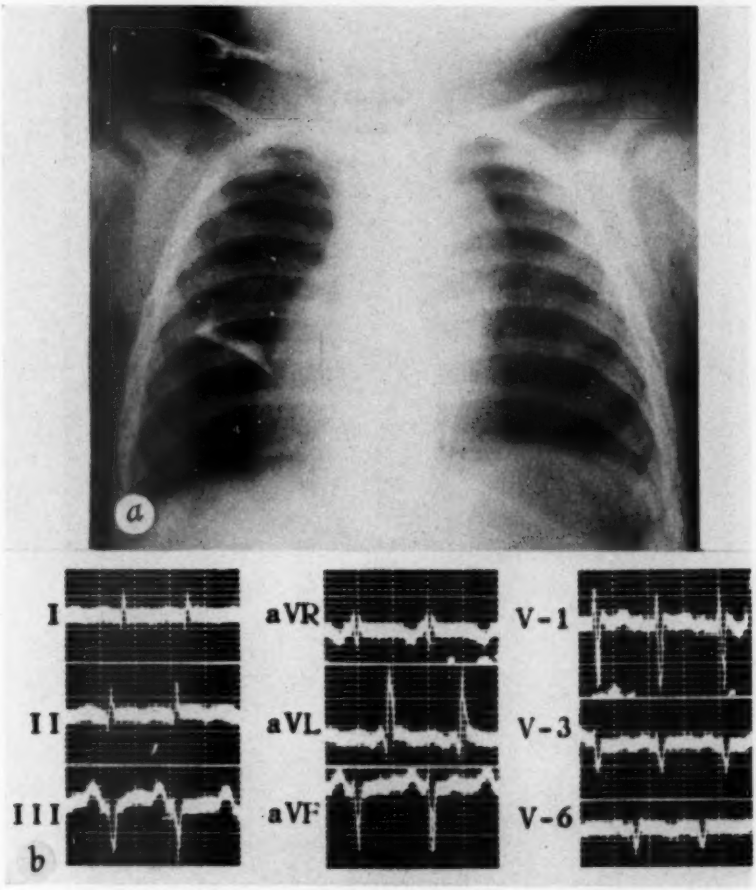

Fig. 1.—(*a*) Roentgenogram of thorax and (*b*) electrocardiogram.

Physical examination when the patient was 6½ months old revealed marked cyanosis, which was intensified when he cried. A loud systolic murmur was heard over the entire precordium; it was loudest to the right of the xiphisternal junction.

Roentgenographic examination revealed dextrocardia and prominence in the region of the anticipated location of the shadow of the pulmonary trunk (Fig. 1*a*). The electrocardiograms were characterized by right axis deviation in the standard leads and negative P waves in both AV_R and AV_L. The P wave in Lead I was isoelectric, while that in Lead III was prominent. The precordial leads were characterized by the development of S deflection over the left pre-

Fig. 2.—(*a*) Anterior view of heart and lungs. Apex of heart is directed to right. A prominence on left side above cardiac shadow seen in roentgenogram (Fig. 1*a*) is probably caused by transposed and wide ascending aorta. (*b*) Base of heart, great vessels, and left lung viewed from left. Pulmonary trunk (*pul. tr.*), which lies behind transposed aorta, is narrow. A ductus arteriosus is present on each side. Aortic arch is in a normal position, arching over left pulmonary hilus. *L.A.*, left atrium; *L.P.A.*, left pulmonary artery; *L.P.V.*, left pulmonary veins; *R.S.A.*, right subclavian artery; *R.C.C.*, right common carotid artery; *L.C.C.*, left common carotid artery; *L.S.A.*, left subclavian artery.

cordium (Fig. 1*b*). The tracings were consistent with or generally indicative of dextrocardia with right ventricular hypertrophy.[2]

Description of Specimen.—From the exterior it was apparent that the apex of the heart lay to the right of the median line and that the great vessels were transposed, the aorta lying anterior and parallel to the pulmonary trunk (Fig. 2, *a* and *b*). The aorta was wide, its diameter being 1.5 cm. The pulmonary trunk was narrow, measuring 3 mm. in diameter. Its lumen

Fig. 3.—(*a*) Base of heart, great vessels, and right lung viewed from right. From short innominate artery, patent right ductus arteriosus is seen entering right pulmonary artery (*R.P.A.*). For other abbreviations, see Figure 2*b*. (*b*) Interior of aorta and associated structures viewed from left. Dimple at aortic entrance of closed left ductus arteriosus is shown.

was correspondingly narrow except at the base of the heart, where the pulmonary trunk was atretic. The aortic arch passed over the left bronchus and blended with the descending aorta, which likewise was in a normal position on the left side. Three branches arose from the aortic arch: the innominate artery, the left common carotid artery, and the left subclavian artery, in that order from ventral to dorsal.

2. Burchell, H. B.: Personal communication to the authors.

The innominate artery was short and gave rise to the right common carotid and the right subclavian arteries. From the terminal portion of the innominate artery a vessel issued which measured 5 mm. in diameter and possessed a lumen of comparable size. The lower end of this vessel terminated in the superior aspect of the right pulmonary artery. The vessel connecting the innominate and the right pulmonary arteries was interpreted as a patent ductus arteriosus on the right (Figs. 2*b* and 3*a*). On the left side a cord-like strand of tissue extended from the

Fig. 4.—(*a*) Thoracic organs, showing details of interior of right side of heart. Right atrium is in normal position and has normal connections. Right ventricular chamber is small and forms only a small part of ventricular portion of heart. There is a ventricular septal defect. (*b*) Interior of left ventricle. Aorta arises entirely from left ventricle and is in close association with ventricular septal defect involving membranous portion of septum. Tricuspid-valve tissue (*T.V.*) is attached to edges of defect. Between these attachments muscular strands cross defect. Mitral valve (*M.V.*) is normal.

lower aspect of the aorta at a point opposite the origin of the left subclavian artery (Fig. 2*a*). This strand was inserted into the superior aspect of the left pulmonary artery. That it represented an obliterated left ductus arteriosus was supported by several facts in addition to that of

its location. At the aortic insertion of the strand the aortic intima showed an elevation at the center of which was a dimple (Fig. 3*b*). The appearance here was consistent with the aortic end of an obliterated ductus arteriosus. The left recurrent laryngeal nerve was observed to hook around the obliterated left ductus arteriosus in a normal manner. When an attempt was made to trace the course of the right recurrent laryngeal nerve, it was found that dissection of the specimen had been carried to a point at which it was impossible to identify the nerve. However, a histologic section prepared from tissue posterior-medial to the structure considered to be a patent right ductus arteriosus revealed nerve fibers.

Examination of the heart revealed that the atria and their venous connections were normal, and the atria lay on the correct sides. In the atrial septum there was a patent foramen ovale guarded by a competent valve. The ventricular portion of the heart was formed mainly by the left ventricle. The right ventricle was but a small chamber lying beside the right upper aspect of the left ventricle (Fig. 4*a*). The right and left ventricular walls each averaged 0.6 cm. in thickness. A defect of the ventricular septum representing absence of the membranous portion was present. Several strands of muscle coursing between the anterior and posterior walls of the outflow portion of the left ventricle lay across the defect (Fig. 4*b*). Tricuspid-valve tissue was adherent to the superior and postero-inferior margins of the ventricular septal defect. The mitral valve was normal and communicated with the left ventricle. The aorta arose in close relation to the ventricular septal defect but entirely from the left ventricle. No opening between the pulmonary trunk and the heart could be found.

The bronchial arteries were moderately dilated. The lungs, including the intrapulmonary vessels, were normal both grossly and histologically. The abdominal organs were in normal position.

COMMENT

The presence of bilateral ductus arteriosus (the right being patent and the left obliterated) seems adequately established for the specimen herein described. It is interesting to discuss the developmental basis for this phenomenon. With regard to the aortic arch system in the case being considered, the pattern was normal but for the addition of a ductus arteriosus on the right side. It already has been stated that at a stage in early development there are right and left sixth (pulmonary) aortic arches. Each pulmonary artery arises as a branch of the sixth arch of its side. The first portion of each sixth arch of the embryo is represented by the origins of each pulmonary artery of the definitive state.

That portion of each sixth arch which lies dorsal to the origin of its pulmonary arterial branch may be considered the ductus arteriosus. On the left side this structure persists. On the right side under normal conditions, on the contrary, the ductus arteriosus disappears at so early a state that no vestige of it can be found in the mature fetus. In our case the presence of the ductus arteriosus on the right side merely represents failure of disappearance of that part of the right sixth arch which lay dorsal to the point of origin of the right pulmonary artery. Otherwise the development of the aortic arch system seemed to have been normal.

Reference to Figure 5 perhaps will give a better understanding of the essential steps in the development of the aortic arch system in the present case. In Figure 5*a* are represented those portions of the aortic arch system of the embryo that are pertinent to this account. These have been modified to resemble in shape the aorta of the adult. At the same time the subclavian arterial origins from the aorta have been indicated as lying cephalad to the sixth aortic arches, in the position found in the adult, which is the reverse of that of the young embryo. It will be seen that there is both a right and a left ductus arteriosus representing the distal portions of the sixth aortic arches. For the development of the normal aorta that portion of the aorta which lies caudal to the origin of the right subclavian artery is interrupted. This interruption converts the definitive right aortic arch into the innominate

artery. The only abnormality of the arch system in our case lies in the fact that the right ductus arteriosus persisted, leading to the pattern represented in Figure 5*b*.

Accounts of total persistence of each sixth aortic arch are scarce. We are familiar with only three earlier references to such cases. Two of these are mentioned in the excellent and comprehensive account of the literature on malformations of the aortic arch system published by Poynter in 1916.[3] In this contribution Poynter stated:

> Persistence of both pulmonary arches is very rare; the only cases with which I am familiar are those of Breschet (1826) and Peacock (1868). In the former the aortic arch was normal, the common pulmonary artery short and from its left branch the ductus arteriosus extended in the usual way. From the right branch of the pulmonary artery a slender artery extended upward to the right, joining the subclavian artery in its proximal portion. In the latter case the development is not so regular.

The third case of which we are aware is that of Ghon,[4] which was described in 1908. This case was reviewed in greater detail by one of us (Edwards) in earlier material.[5]

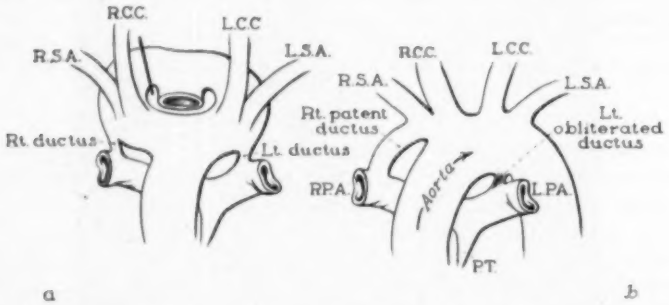

Fig. 5.—(*a*) Pertinent portions of aortic arch system of embryo portrayed to resemble adult structure. In right aortic arch beyond right subclavian artery, heavy line indicates break in aortic arch system which led to malformation of aortic arch (*b*) in case described.

There is still another group of cases which, although not identical with those under discussion, are related to them. These were reported by Fraentzel,[6] Doering,[7] Ambrus,[8] and Jew and Gross.[9] Each of the specimens was characterized by the

3. Poynter, C. W. M.: Arterial Anomalies Pertaining to the Aortic Arches and the Branches Arising from Them, Studies Zool. Lab. Univ. Nebraska **16**:229 (Oct.) 1916.

4. Ghon, A.: Über eine seltene Entwicklungsstörung des Gefässsystems, Verhandl. deutsch. path. Gesellsch. **12**:242, 1908.

5. Edwards, J. E.: Congenital Cardiac Disease, in Gould, S. E.: Pathology of the Heart, Springfield, Ill., Charles C Thomas, Publisher, to be published; Malformations of the Aortic Arch System Manifested as "Vascular Rings," Lab. Invest., to be published.

6. Fraentzel, O.: Ein Fall von abnormer Communication der Aorta mit der Arteria pulmonalis, Arch. path. Anat. **43**:420 (May 27) 1868.

7. Doering, H.: Angeborener Defekt der rechten Lungenarterie, Studien Path. Entwicklung **2**:41, 1914.

8. Ambrus, G.: Congenital Absence of the Right Pulmonary Artery with Bleeding into the Right Lung, J. Tech. Methods **15**:103 (March) 1936.

9. Jew, E. W., Jr., and Gross, P.: Aortic Origin of the Right Pulmonary Artery and Absence of the Transverse Aortic Arch: Associated with Patency of the Interventricular Septum and the Ductus Arteriosus, A. M. A. Arch. Path. **53**:191 (Feb.) 1952.

pulmonary trunk's continuing as the left pulmonary artery while the right pulmonary artery did not arise from the pulmonary trunk but from the innominate artery. On the left side a ductus arteriosus extended from the left pulmonary artery to the aorta. In each of these cases it is evident that the entire left sixth aortic arch was present. It is likely that on the right side the entire sixth arch had been present but that its proximal portion had disappeared after the right pulmonary artery had arisen. The channel between the innominate artery and the right pulmonary artery is to be considered as the right ductus arteriosus. To reiterate, in the latter cases it seems that the portion of the right sixth aortic arch which normally remains had disappeared and that that part of the right sixth arch which normally disappears had remained. These cases may be classified as examples of bilateral ductus arteriosus, but they do not fulfill entirely the designation of persistence of each sixth aortic arch.

Brief comment should be made about the functional significance of the cardiac malformations. Anatomically there was in essence atresia of the origin of the pulmonary trunk and a ventricular septal defect. The only avenue for the blood that entered the right ventricle was this defect, through which the blood flowed from this chamber into the left ventricle. In the latter chamber the venous blood mixed with the oxygenated blood which entered through the mitral valve. The mixture of blood in the left ventricle escaped into the aorta. From this vessel the systemic circulation was supplied with incompletely oxygenated blood. The arterial avenues for blood flow to the lungs were the patent right ductus arteriosus and enlarged bronchial arteries. It is apparent that while there were two ventricles the heart functioned as though only a common ventricle existed, the left ventricle assuming this function.

The dextrocardia which was present in this case should be classified as isolated dextrocardia, since the remaining organs were in their normal positions.[10]

The presence of serious malformations of the heart with isolated dextrocardia, as in this case, is common. Lichtman,[11] who reviewed 161 cases of isolated dextrocardia, found only 3 in which there was no other defect of the heart.

SUMMARY

After death of a boy 10 months of age, bilateral ductus arteriosus was found, accompanied by isolated dextrocardia, ventricular septal defect, and pulmonary atresia.

The left ductus arteriosus was obliterated in a normal manner, while the right ductus arteriosus was patent and served as a collateral channel for pulmonary blood flow.

The occurrence of a ductus arteriosus on each side represents persistence of each sixth aortic arch of the embryo. This malformation of the aortic arch system is rare.

10. Chapman, C. B., and Gibbons, T. B.: New Aids in the Diagnosis of Dextrocardia, Am. Heart J. **39**:507 (April) 1950.

11. Lichtman, S. S.: Isolated Congenital Dextrocardia: Report of 2 Cases with Unusual Electrocardiographic Findings; Anatomic, Clinical, Roentgenologic, and Electrocardiographic Studies of the Cases Reported in the Literature, Arch. Int. Med. **48**:683 (Nov.) 1931.

PRIMARY ALVEOLAR CELL CARCINOMA OF THE LUNG

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ALVEOLAR cell tumors of the human lung are decidedly uncommon. In 1942 Neubuerger and Geever [1] critically reviewed the literature on this subject. They collected 25 authentic cases from the literature and added 2 of their own. In 1949 Swan,[2] in screening approximately 900 pulmonary neoplasms at the Army Institute of Pathology, encountered nine pulmonary tumors which had not been previously reported and which fulfilled the criteria established for tumors of this type. The criteria which Swan laid down for these tumors are these: tall columnar mucus-secreting cells lining the pulmonary alveoli; absence of an intrinsic tumor of the bronchi, and absence of a primary adenocarcinoma of any other part of the body.

Shortly after Swan's publication, Laipply and Fisher [3] again reviewed the literature and reported two cases of primary alveolar cell carcinoma of their own. They pointed out that up to that time 30 cases of malignant alveolar cell tumor of the lung, including their own, had been reported in man.

From 1949 to the present time at least 14 additional papers have been published on this subject, most of them reporting one or two cases or small series of cases. The largest series, 33 cases, reported from any one center is that recently published by Watson and Smith,[4] from Memorial Hospital in New York.

The purpose of this paper is to review briefly and report five cases of malignant alveolar cell tumor of the lung. Brief reference is made to a sixth case, which is believed to be an authentic one, but the man is still alive and consequently the diagnosis has not been proved.

REPORT OF CASES

CASE 1.—A white woman aged 80, complained of dyspnea and pain in her chest. She said she thought she suffered from bronchitis. She had lost considerable weight during the past few months and when first seen was moderately emaciated. She had undergone a hysterectomy for uterine fibroids 20 years before. X-ray studies of the chest revealed a large quantity of fluid

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1. Neubuerger, K. T., and Geever, E. F.: Arch. Path. **33**:551, 1942.
2. Swan, L. L.: Arch. Path. **47**:517, 1949.
3. Laipply, T. C., and Fisher, C. I.: Arch. Path. **48**:107, 1949.
4. Watson, W. L., and Smith, R. R.: J. A. M. A. **147**:7, 1951.

in the right pleural space. The radiologist stated that fairly extensive fibrosis was present in the upper lobe of the right lung, but he was unwilling to express an opinion as to the nature of the abnormal findings. He stated that the left lung showed no lesions. Large quantities of blood-tinged fluid were removed from the right pleural space on repeated occasions. Malignant tumor cells were demonstrated in this fluid. The patient became more emaciated and weaker quite rapidly and died after an illness of about two months.

At autopsy the right pleural space contained 2,000 cc. of reddish-brown fluid. The visceral and parietal pleura on the right side was markedly thickened and chocolate-colored. It and the diaphragm were infiltrated with tumor growth. There were no adhesions and no effusion in the left pleural space. The right lung weighed 270 gm. and was atelectatic throughout. The interlobar fissures were obliterated completely with adhesions. Discrete small white nodules were distributed through the pulmonary tissue. The hilar nodes were enlarged and invaded with tumor growth. The left lung weighed 275 gm. It was emphysematous. Small discrete white tumor nodules were distributed widely throughout the lung, and a few similar nodules were present on the visceral pleural surface. The bronchial tree was free from tumor involvement. The autopsy was a partial one; examination of the abdominal organs through the incison revealed no tumor involvement of them, but they were not removed for further study.

Case 2.—A Japanese man aged 47 was admitted to a sanatorium complaining of cough, expectoration, and pain in the lower left chest and later in the left shoulder region. He stated that he had been perfectly well until a few days before admission when he caught "a cold" which did not clear up. Clinical and laboratory investigations revealed no positive evidence of tuberculosis. X-ray studies of his chest showed innumerable stippled areas of increased density in both lung fields (Fig. 4). Miliary tuberculosis, pulmonary mycosis, and metastatic carcinoma were suggested as possible diagnoses, the latter being the most probable. The patient's course was progressively downhill, with dyspnea, cyanosis, some fever, wheezing respirations, weakness, loss of weight, and death less than three months after the onset of symptoms.

At autopsy, the right and left pleural spaces contained 200 cc. and 250 cc. of slightly blood-tinged fluid respectively. The lungs were voluminous, nearly completely filling the pleural spaces. The right lung weighed 1,050 gm. Innumerable miliary grayish-white nodules were seen and felt on the external surface of the lung, and on section the cut surface throughout the lung was studded with similar nodules. No endobronchial tumor or ulceration was found. The left lung weighed 1,050 gm. and was closely similar to the right. Metastases were present in the hilar, mediastinal, and abdominal lymph nodes, liver, left kidney, adrenals, ribs, and vertebrae.

Case 3.—A 61-year-old white man complained of dyspnea, wheezing respirations, and productive cough, without hemoptysis. These symptoms were present for about a month. He had a secondary anemia. X-ray studies of his chest revealed diffuse mottling of both lung fields suggestive of miliary tuberculosis, but it was thought that the nodules were too large for this disease and pulmonary mycosis was suggested as a more probable diagnosis. He became very weak and deteriorated rapidly. He got out of bed one morning, collapsed, and died in a few minutes.

At autopsy there were no pleural adhesions, but because the body had been embalmed it was impossible to tell about pleural effusion. Both lungs were voluminous. The right weighed 950 gm. and the left 966 gm. They were closely similar in appearance. Innumerable small discrete and larger confluent white nodules were widely scattered throughout the lungs. In some parts, especially the upper lobe of the left lung, the tumor growth was diffuse and grossly not unlike lobar pneumonia. It was remarkably free from necrosis. The bronchi were uninvolved with tumor growth. Metastases were present in the hilar and mediastinal lymph nodes, the pericardium, and the eighth left rib; there was a single tiny nodule in the liver, and a microscopic focus of tumor cells in the spleen.

Case 4.[5]—The patient was a 54-year-old white woman whose illness, which she thought was bronchitis, started about six months before she first sought medical advice. A month prior to that time a "chest cold" had developed which aggravated her symptoms, and she noticed that she was short of breath on exertion. Six weeks later she was admitted to the hospital, at which time she complained of increasing dyspnea and an unproductive cough made worse by lying

5. This case is reported through the courtesy of Dr. D. F. Plewes, Brantford, Ont., Canada.

down. X-ray examination of her chest revealed widespread rather fine mottling of both lung fields. From the x-ray appearance a diagnosis of pulmonary adenomatosis was suggested. The patient died about 10 months after the onset of symptoms.

At autopsy (W. J. H.) the right and left pleural spaces contained 1,500 and 1,000 cc. respectively of clear yellow fluid. Both lungs were voluminous. The left lung weighed 577 gm. The cut surface of both upper and lower lobes was studded with extremely numerous small discrete and confluent grayish-white nodules (Fig. 2). The right lung weighed 763 gm. Its upper and middle lobes were diffusely consolidated and resembled lung tissue in lobar pneumonia except that the tissue felt firmer and its cut surface was not granular. The lower lobe of the right lung contained innumerable small widely scattered nodules and resembled the left lung. Dissection revealed no intrinsic tumor of the bronchial tree. Metastases were present in the hilar lymph nodes of both lungs.

Case 5.[6]—A white man aged 62 had been a wool weaver in the carpet-manufacturing business for over 50 years. About five months prior to the onset of symptoms, x-ray films of his chest taken during a chest survey were passed as within normal limits. His illness began with weakness, pain in the chest, wheezing, and cough with scanty sputum. X-ray studies of his chest were repeated; a provisional diagnosis of miliary tuberculosis was made, and he was admitted to a sanatorium. At that time on x-ray examination a scattered, densely mottled infiltration was seen throughout both lung fields. He had lost some weight. His temperature was slightly elevated, and his blood sedimentation rate was 51 mm. A month later a chest film showed bilateral extension of the disease. Fungus infection of the lungs, miliary tuberculosis, and carcinomatosis were the diagnoses considered, with the latter thought to be the most likely. The patient's weakness and dyspnea became progressively worse, and he died at home about three months after the onset of symptoms.

At autopsy (W. J. H.) the pleural spaces were largely obliterated with adhesions. There was no pleural effusion. The left lung weighed 723 gm. Its cut surface was studded with discrete and confluent grayish-white nodules. The right lung weighed 1,161 gm. It showed areas of diffuse consolidation with tumor growth and areas in which the tumor growth showed a finely nodular appearance. The bronchi revealed no evidence of tumor growth. Metastases were present in the hilar lymph nodes of both lungs, in the pericardium, and in the sternum.

Case 6.—Since the preparation of this paper, a sixth case has been encountered, that of a man, 47 years old, with a scattered, finely mottled infiltration of both lung fields and with invasion of his fifth lumbar vertebra and right supraclavicular lymph nodes. Biopsy of the vertebra and a lymph node showed a histologic appearance highly suggestive of primary alveolar cell carcinoma of the lung. Since this man is still alive, the diagnosis has not been proved by autopsy, but this is considered to be an authentic case of primary alveolar-cell carcinoma of the lung.

PATHOLOGIC FEATURES

Gross.—The pleural cavity contained fluid in three of the five cases and probably contained fluid in a fourth, although this point could not be definitely verified because the body had been embalmed. The fluid was sanguineous in two. Extensive fibrous pleural adhesions were present in one case. In all five cases both lungs were involved with tumor growth. The lungs usually were voluminous and firm; they did not collapse, and individual lungs varied in weight from 270 to 1,161 gm. The visceral pleural surface usually was studded with tumor nodules and, except for the color and contour, looked not unlike a hobnail liver (Fig. 1). The distribution of the tumor growth in the lung was nodular, diffuse, or a combination of these two forms. In the nodular type innumerable discrete and confluent grayish-white tumor nodules, varying in diameter from miliary size to 1 cm. or more in diameter, were widely scattered throughout the lung parenchyma. In the diffuse

6. This case is reported through the courtesy of Dr. F. D. Clarke, Brantford, Ont., Canada.

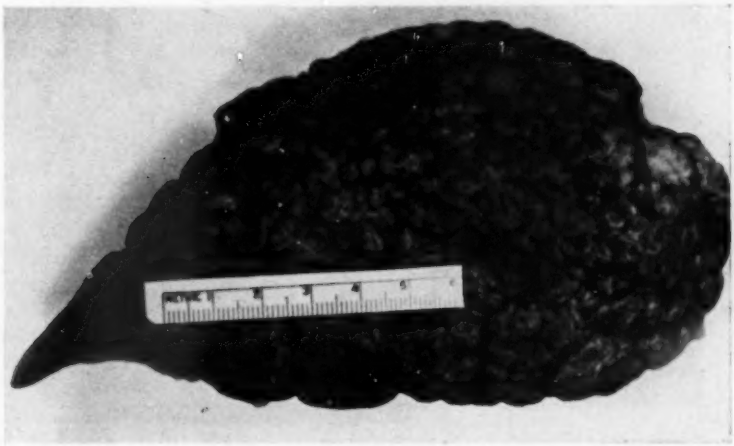


Fig. 1 (Case 4).—Pleural surface of the upper lobe of the left lung, showing the nodular appearance of the tumor growth.

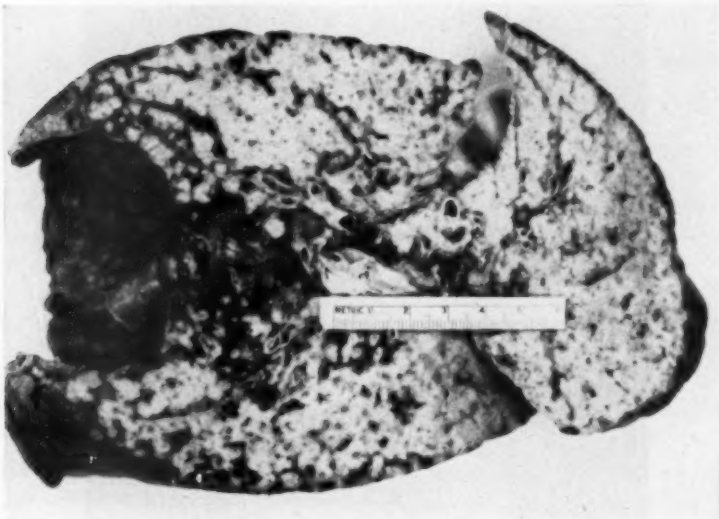


Fig. 2 (Case 4).—Cut surface of the upper and lower lobes of the left lung, showing innumerable discrete and coalescent tumor nodules.

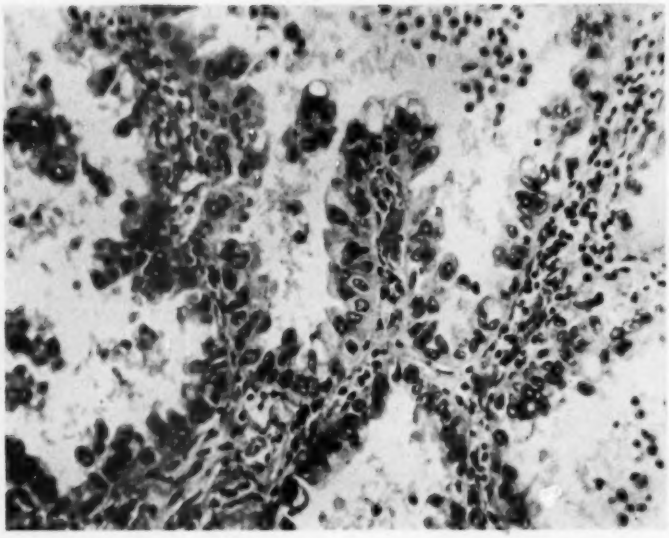


Fig. 3 (Case 3).—Pulmonary alveoli lined with closely investing, tall columnar cells; tumor papillae project into the alveolar spaces; × 230.

Fig. 4 (Case 2).—Roentgenogram of the chest showing widely scattered, finely mottled infiltration of both lungs.

form extensive areas of lung tissue or a whole lobe were uniformly consolidated with tumor growth resembling the gray hepatization of lobar pneumonia except that the involved lung tissue felt firmer than in lobar pneumonia and its cut surface was not granular. In no instance was gross necrosis observed in the tumor tissue. The anatomic types and distribution of metastases are outlined in the accompanying Table.

Microscopic.—Many of the microscopic characteristics were common to all five cases. The most striking feature was the unique pattern of growth. Tall cuboidal, columnar, or cylindric cells lined the pulmonary alveoli, in most instances forming a single layer of closely investing cells with a gently serrated border. In some instances, papillary projections of tumor cells jutted into the alveolar spaces (Fig. 3). The slightly to markedly thickened alveolar walls formed the stroma of the tumor. The tumor cells were not desmoplastic. They showed little pleomorphism. The nuclei were round or oval and occasionally vesicular. The chromatin, stained pink to red with Masson's trichrome stain, was usually powdery and evenly

Data from Six Cases of Primary Alveolar Cell Carcinoma of Lung

Case	Sex	Age, Yr.	Lung Involvement	Anatomic Type	Metastases
1	F	80	Bilateral	Multiple nodular	Pleura, diaphragm bronchial nodes (autopsy limited to thorax)
2	M	47	Bilateral	Multiple nodular	Bronchial and retroperitoneal nodes, liver, left kidney, adrenals, ribs, and vertebrae
3	M	61	Bilateral	Nodular and diffuse	Bronchial and mediastinal nodes, pericardium, liver, spleen, rib
4	F	54	Bilateral	Nodular and diffuse	Hilar lymph nodes
5	M	62	Bilateral	Nodular and diffuse	Hilar lymph nodes, pericardium, sternum
6	M	47	Bilateral	Multiple nodular	Vertebra, right supraclavicular lymph nodes*

* These are biopsy observations; the patient is still alive.

scattered. A single nucleolus stained pink to red with Masson's stain. In case 4 some of the tumor cells appeared to be ciliated (Fig. 6), but in all other instances no cilia were seen. The alveolar spaces contained desquamated tumor cells, macrophages, and some leucocytes. Mucin was demonstrated in the tumor cells and alveolar spaces, the latter in some instances (Cases 2 and 5) being filled with pools of mucin which stained red with mucicarmine. The tumor growth in all instances was richly vascularized. Necrosis was noticeably lacking, and the alveolar walls remained remarkably intact. Freedom of the bronchi from tumor participation was an outstanding feature in all sections. In all five cases the tumor was definitely malignant. In one case (case 1) some of the tumor nodules revealed a strikingly papillary adenomatous appearance resembling closely the lesions of jagziekte in sheep (Fig. 5). The predominating cell in all cases appeared to be epithelial in type. The tumor readily infiltrated lymph channels. The pattern of growth, its general appearance, and its behavior were those of a carcinoma. In its metastases the original characteristics of the tumor cells and their pattern of growth were often remarkably retained. In lymphatics they often lined the channels in a striking manner.

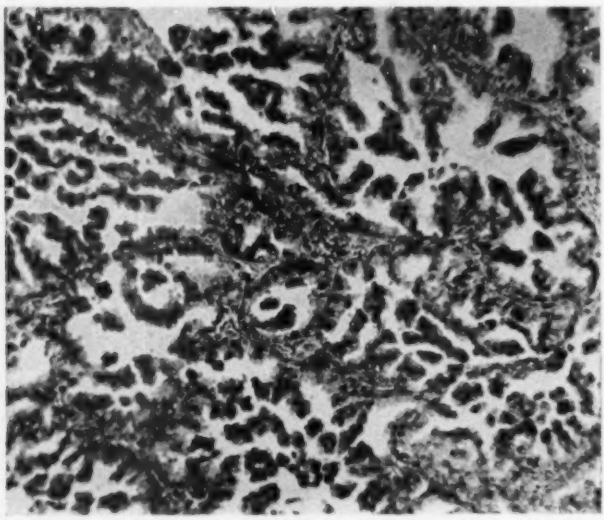


Fig. 5 (Case 1).—Nodule of pulmonary adenomatosis resembling closely jagziekte in sheep; × 120.

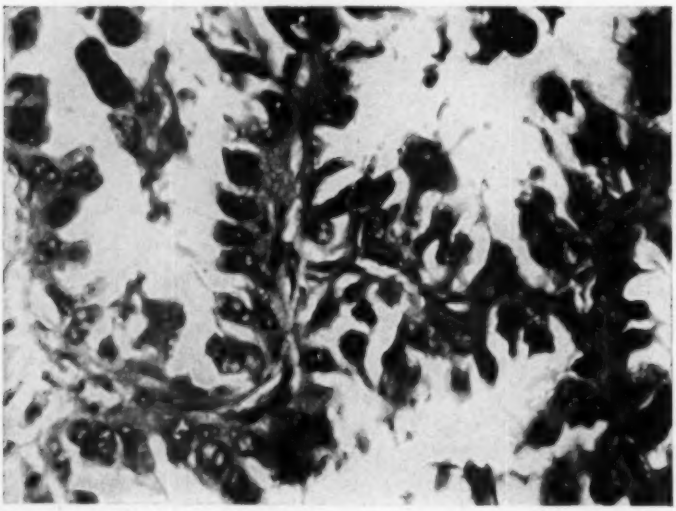


Fig. 6 (Case 4).—Detail of tumor cells. Some of the tumor cells are ciliated; × 460.

COMMENT

The clinical signs and symptoms were those of a chronic pulmonary disease and not peculiar to this type of tumor. Cough, usually with little expectoration, pain in the chest, dyspnea, wheezing respirations, and weakness were common complaints. Pleural effusion was present in four of the five cases. In reviewing the clinical histories of the five cases reported in this paper, one gets the impression that the clinical course is much shorter than in other cases of untreated malignant pulmonary neoplasms. This observation corresponds to the experience of Watson and Smith.[4] None of the patients received x-ray therapy. In Case 4 the duration of life was about 10 months, while in the other four cases all the patients were dead within three months of the onset of symptoms.

The x-ray findings in the chest are not pathognomonic of this disease. However, in all the cases, except Case 1, the chest films revealed a scattered, densely mottled infiltration of both lung fields, for which miliary tuberculosis, pulmonary mycosis, and carcinomatosis were considered as possible diagnoses. In Case 4 a diagnosis of pulmonary adenomatosis was suggested on the strength of the x-ray picture.

In all cases increasing dyspnea was a prominent symptom. When one sees the widespread tumor growth lining innumerable pulmonary alveoli in both lungs, serious interference with normal pulmonary function is to be expected. It is believed that this was an important contributory cause of death. Evidence of right heart failure was not observed.

It is unfortunate that bronchial secretions were not examined for malignant cells in any of these cases, but some of them occurred at a time when exfoliative cytology was not commonly employed. It is also regrettable that the brain was not examined in any of these cases.

Structures believed to be cilia were associated with the tumor cells in Case 4 (Fig. 6). Only 3 other cases [7] have been reported in the literature in which the cells of this type of tumor have been ciliated. In Case 1, some of the tumor nodules closely resembled the histologic picture of jagziekte in sheep.

The histogenesis of these tumors remains controversial. However, the term "alveolar cell tumor" of the lung has been used to designate them. According to the recent investigations of Short [8] and of Ham and Baldwin,[9] the pulmonary alveoli are derived from mesenchyme which caps the bronchial buds and thus are of mesodermal origin, while the bronchial epithelium is of entodermal derivation. The alveolar epithelium ceases to exist after a certain period of embryonic life. The terminal bronchiolar epithelium comes to an end abruptly and is replaced by the lace-like structure of the alveolar septum. If these observations are true, it would seem most unlikely that these tumors arise from alveolar epithelium. All tumors here reported are malignant. Since the tumor cells secrete mucin, since they are sometimes ciliated, and since their cytologic features, pattern of growth, and distribution of metastases resemble those of a carcinoma, it is my opinion that they are epithelial in nature and that they originate in the terminal bronchiolar epithelium.

7. Swan,[2] Laipply and Fisher,[3] Paul, L. W., and Ritchie, G.: Radiology **47**:334, 1946.
8. Short, R. H. D.; Philos. Tr. Soc. London, Ser. B: Biol. Sc. **235**:35, 1950.
9. Ham, A. W., and Baldwin, K. W.: Anat. Rec. **81**:363, 1941.

This is in agreement with the views of Watson and Smith,[9] Herbut,[10] Ikeda,[11] and Bonne.[12] Since the tumor in its advanced stage was distributed so widely throughout both lungs, it was impossible to determine its exact site of origin. However, it is probable that it arose from multicentric foci; otherwise it is difficult to explain the pathway of dissemination in both lungs. Nevertheless, the absence of demonstrable bronchial involvement, the unique histologic pattern, and the peculiar gross anatomic features are not seen in other bronchogenic tumors. These characteristics would seem to warrant placing this tumor in a separate category.

SUMMARY

Five cases of so-called primary alveolar cell tumor of the lung are reported, and a probable sixth case is mentioned briefly. All the tumors were malignant, producing regional or distant metastases. In all cases both lungs were involved. In 3 the tumor was multiple nodular in type, while in the other 3 it was combined nodular and diffuse. The histologic structures of the two anatomic forms of the tumor are identical. In structure and biologic behavior the tumors resembled a carcinoma. For reasons presented, the opinion is expressed that these tumors arise from terminal bronchiolar epithelium. Others have called them "cancerous pulmonary adenomatosis." No case of benign pulmonary adenomatosis has been encountered in this investigation.

In all instances the tumor fulfilled the criteria set forth by Swan. The gross and microscopic features corresponded closely to those described by Swan and by Neubuerger and Geever. The combination of its unique histologic structure, its gross characteristics unusual for other pulmonary neoplasms, and its more or less constant roentgenologic picture serves to place this tumor in a separate category.

No constant factor has been encountered in the clinical histories which seem to bear a causal relationship to the tumor.

The ratio of males to females was 4:2. The patients' ages ranged from 47 to 80. In all six cases the clinical signs and symptoms were those of a chronic pulmonary disease. It is considered that the widespread tumor growth in the lungs interfered with normal pulmonary function and thus was an important contributory cause of death.

10. Herbut, P. A.: Arch. Path. **41**:175, 1946.
11. Ikeda, K.: Am. J. Clin. Path. **15**:50, 1945.
12. Bonne, C.: Am. J. Cancer **35**:491, 1939.

News and Comment

ANNOUNCEMENTS

International Association of Medical Museums.—The annual meeting of the International Association of Medical Museums will be held at the New Hotel Jefferson, St. Louis, March 31-April 1, 1953, immediately preceding the meetings of the American Association of Pathologists and Bacteriologists.

A course in pathological physiology of the lung will be given on Tuesday, March 31. Included in the program will be a discussion of the embryology, anatomy, and physiology of the lung; the infectious, neoplastic, and experimental aspects of the lung diseases; pulmonary diseases of infants and children, and lung diseases of animals. On Wednesday, April 1, there will be a symposium on techniques for the demonstration of structural changes in tissue following the use of modern chemotherapeutic agents.

All pathologists are cordially invited to attend.

American Board of Pathology.—The written and practical examinations in pathologic anatomy and clinical pathology of the American Board of Pathology will be given March 28, 30, and 31, 1953, Washington University School of Medicine, St. Louis. The examinations will include exfoliative cytology.

Books

Chemical Physiology of Endoparasitic Animals. By Theodor von Brand, Laboratory of Tropical Diseases, National Institutes of Health, U. S. Public Health Service, Bethesda, Md. Price, $7.50. Pp. 339, with 41 tables. Academic Press, Inc., 125 E. 23rd St., New York 10, 1952.

Die Krankheiten der Nasennebenhöhlen, der Ohren und des Halses im Röntgenbild (45. Ergänzungsband der "Fortschritte auf dem Gebiete der Röntgenstrahlen vereinigt mit Röntgenpraxis"). By Prof. Dr. Richard Mittermaier, director of the university ear, nose, and throat clinic, Marburg. Second edition. Price, 66 German marks. Pp. 232, with 483 illustrations. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart-O; agents for U. S. A.: Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1952.

Der Gesunde und der Kranke Kehlkopf im Röntgenbild. By Prof. Dr. C. R. Griebel. Price, 48 German marks. Pp. 170, with 156 illustrations. Georg Thieme, Diemershaldenstrasse 47, (14a), Stuttgart-O; agents for U. S. A.: Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1952.

Experiments on the Oxytocin Sensitivity of the Rat Uterus. By Erik Brandt-Nielsen. Paper bound. Pp. 240, with 20 illustrations. Price, not given. Det Danske Forlag, Copenhagen, 1951.

Transplantation of Leukemia into Mice and Its Genetic Aspects. Georg Hogreffe. Paper bound. Pp. 95, with illustrations. Price, not given. P. Haase and Son, Copenhagen, 1951.

Die Osteomalazie. By Dr. Markus Wernly, Bern. Price, 14.40 German marks. Pp. 101, with 16 illustrations. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart-O; agents for U. S. A.: Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1952.

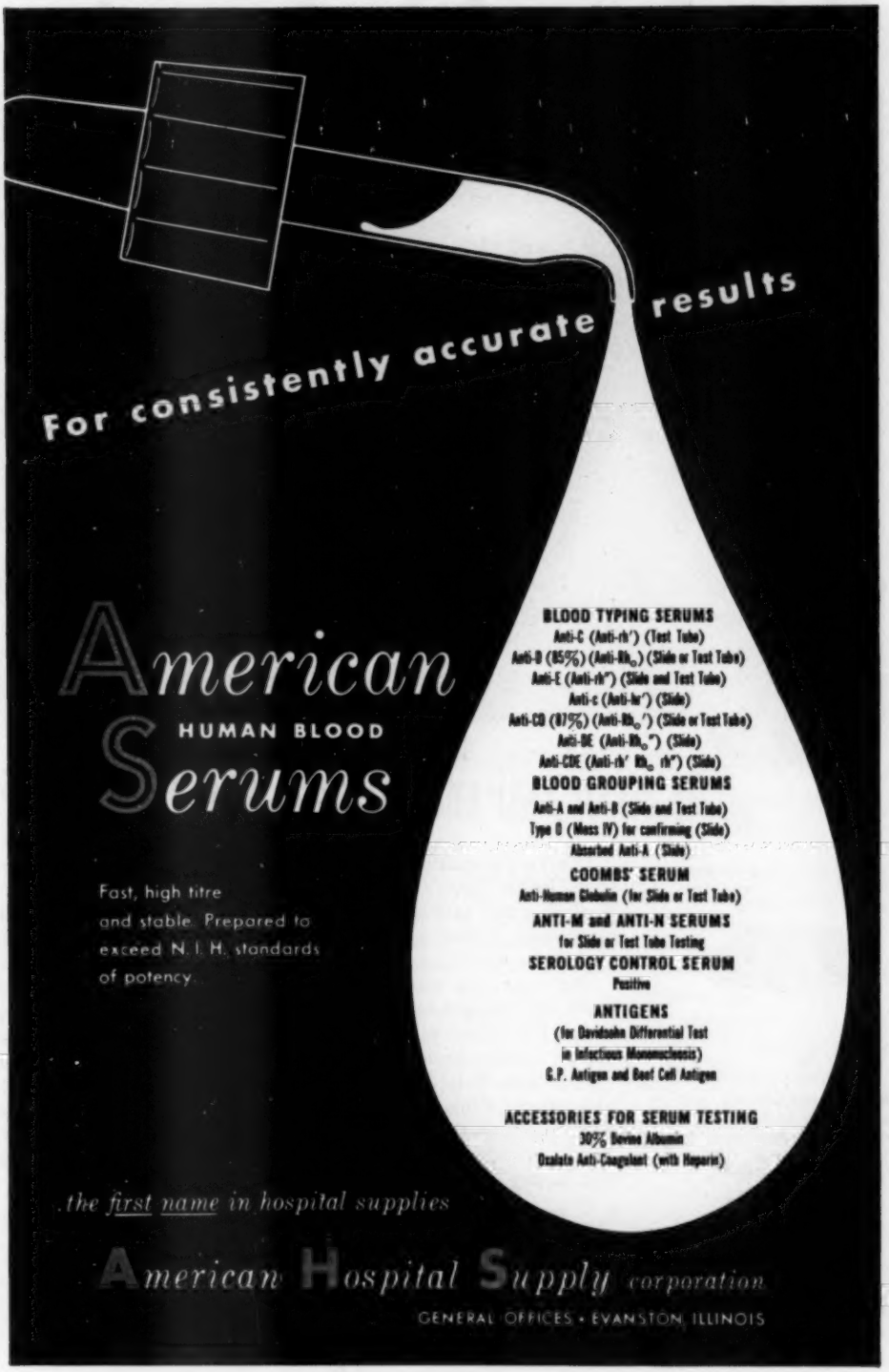
Analyse physico-chimique des eaux de consommation. By Dr. Gaston Sirjean. Price, 800 francs. Pp. 174, with 7 tables. L'Imprimerie Nouvelle, Paris, 1952.

The Treatment of Injuries to the Nervous System. By Donald Munro, M.D., F.A.C.S., surgeon-in-chief, department of neurosurgery, The Boston City Hospital; associate professor of neurosurgery, Boston University School of Medicine; assistant professor of neurosurgery, Harvard University Medical School. Price, $7.50. Pp. 284, with 47 illustrations and 9 tables. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1952.

Anurie bei Chromoproteinurie (Hämolyseniere, Crush-Niere). By Prof. Dr. Hans U. Zollinger. Price, 14.70 German marks. Pp. 138, with 42 illustrations. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart-O; Agents for U. S. A.: Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1952.

Culdoscopy: A New Technique in Gynecology and Obstetric Diagnosis. By Albert Decker, M.D., D.O.G., F.A.C.S., clinical professor of gynecology and obstetrics, New York Polyclinic Medical School and Hospital; associate attending physician in gynecology and obstetrics, New York Polyclinic Hospital; attending gynecologist, Knickerbocker Hospital. With a foreword by Richard W. TeLinde, M.D. Price, $3.50. Pp. 148, with 50 figures. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1952.

Analyse bacteriologique des eaux de consommation. By Dr. Gaston Sirjean. Price, 1200 francs. Pp. 220. L'Imprimerie Nouvelle, Paris, 1952.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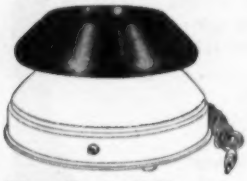

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1. Schilling, F. J.; De Natale, A.; and Mottram, F. C.: Am. J. M. Sc. *222*:207 (Aug.) 1951. 2. Shapiro, S., et al.: Am. Heart J. *40*:766 (Nov.) 1950. 3. Shapiro, S., and Weiner, M.: J. M. Soc. New Jersey *48*:1 (Jan.) 1951.

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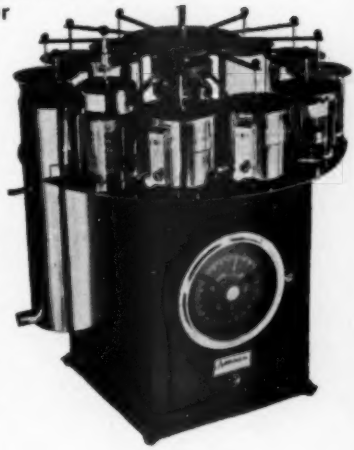

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